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THE EFFECT OF CASTRATION ON THE ANTERIOR HYPOPHYSIS OF THE FEMALE RAT[1]

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Although changes following castration were described in the anterior pituitaries of cattle, buffaloes and fowls as early as 1905 (Fichera), the earliest investigation on the effect of castration on the anterior pituitary of the albino rat was that of Zacherl reported by Biedl in 1912. He described an increase in the volume of the organ and a diminution in the number of acidophiles, but of most interest was his description of a new cell type which he designated as a castration cell. He did not determine the origin of this new cell type.

Addison in 1917, using male rats, presented a more complete histological analysis of the changes occurring in the anterior hypophysis after castration. He described an early increase in the number and size of the basophiles, the larger ones becoming vacuolated in two months after castration. With the increase in the size and number of these vacuoles, the cytoplasm and nuclei were pushed to the side, producing the typical castration cell or "signet-ring" cell. Colloid filling the hypophyseal cleft was found in many of the castrated animals. An increase in size of the anterior lobe capillaries was also mentioned.

Nukaryia (1926) described a marked increase in the number of the typical basophiles in the rat and their modification into castration cells. He was the first to make differential cell counts. His average for normal males was 31.4 per cent eosinophiles, 14.1 per cent basophiles and 54.5 per cent "Hauptzellens" or chromophobes. For the female, his findings were essentially the same, except for a slightly higher basophilic percentage, namely 15.5. In his studies on the effect of castration, limited to male rats, he reported a progressive increase of basophilic elements up to 48.8 per cent at 9 months and 1 week. (The basophiles and castration cells were counted

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together.) He found no changes in the percentage of eosinophiles, but there was a decrease in chromophobes, inversely proportional to the increased percentage of the basophilic cells. He also demonstrated definite localized areas of special cellular predilection.

Satwornitzkaja (1927) also considered that there was an increase in the basophiles in the pituitary following castration. Shenk (1927) studied the changes following castration in the cat, rabbit and rat; he found no change in the first two species, but in the latter a progressive increase in the number of basophilic elements was observed. The "signet-ring" castration cells were described as arising from basophiles, similar to the work of Addison and Nukaryia. Lehman (1928) found a marked increase in the eosinophiles, a slight increase in the basophiles and a decrease in the chromophobes. Stein (1933) completely cited the literature concerning castration changes in many species. In his own studies this investigator found an increase in the relative weights of the pituitaries of male rats following removal of the gonads. Histologically, the experimental animals showed many large basophiles and castration cells. He considered the latter as modified basophiles. A great number of eosinophiles and relatively fewer neutrophiles were found. No cell counts were made. Colloid was found in the residual cleft of the experimental animals. Severinghaus (1933), in a study of the Golgi apparatus of pituitary cell types, considered that a similar type of Golgi apparatus was present in both the castration cells and basophiles. From this he concluded that castration cells were modified basophiles (confirming the view of previous writers). He also reported an increase in basophiles and a slight reduction in eosinophiles in male rats. A progressive decrease in the size of the eosinophiles was noted up to 46 days, following castration (male rats were used).

From this short review it seems fairly definite that castration in rats leads to an increase in the relative number and size of the basophilic elements, which become modified and give rise to the so-called castration cells. However, there appears to be a divergence of opinion as to whether there are changes in the eosinophiles. Since the rat is used extensively in sex research, we have thought it of interest to study the effects of castration in both male and female rats at definite intervals after castration. These studies have been both quantitative and qualitative; differential cell counts have been combined with an analysis of the morphological changes. The anterior pituitaries have been studied at definite intervals following removal of the gonads, in order that a sequence of changes could be correlated. Such studies have been carried out in both male and female rats.

Such studies are of considerable importance to us in that they will serve as an adequate control for a series of experiments which are being carried out in this laboratory and which have as their objective the determination of the effect of various sex hormones on the anterior hypophysis. In this communication we are presenting only our castration studies on female rats.

MATERIALS AND METHODS

Animals used in the experiment were adult virgin female rats weighing at least 150 grams before castration. All animals were bred in our colony. The animals were sacrificed at the following intervals after the removal of the ovaries: 5, 10, 15, 20, 30, 60, 90, 120, 180, 237 and 500 days. One hundred rats were used. At sacrifice the animals were anaesthetized with chloroform, and bled quickly by heart puncture. The hypophysis was removed, and immediately weighed on a torsion balance (Hartmann-Braun, accurate to 0.5 milligrams), and immediately placed in Regaud's fixative. The accessory reproductive organs were fixed in Bouin's fluid, stained and examined routinely. In an attempt to ascertain possible changes in the weight of the pituitary after castration, a factor relating the size of the hypophysis to the body weight has been used. This factor has been calculated by dividing the pituitary weight in milligrams by the body weight in grams and multiplying the quotient by 1,000. The result expresses a quantitative relationship between pituitary weight and body weight.

The hypophyses were prepared for histological study according to the technique described by Cleveland and Wolfe (1932). Sections were cut in a horizontal plane at 2 micra and one section out of every ribbon of 20 was mounted and stained. Utilizing the method of Rasmussen and Herrick (1921), cell counts were made on every fifth field of the five sections studied on each gland. These five sections were carefully selected as representative of various levels of the glandular tissue. In these studies cell counts were made on 506 sections. A total of 286,218 cells was counted.

A few normal females were sacrificed at the several stages of the normal cycle; namely, prooestrus, oestrus, metoestrus and dioestrus.[3] The findings on these pituitaries conformed well with the analysis of the cyclic histologic variations in the normal female rat recently published by Wolfe and Cleveland (1933). Therefore the work of these investigators has constituted control material for comparison with the pituitaries of the castrated female rats.

RESUME OF THE HISTOLOGY OF THE NORMAL FEMALE RAT CORRELATED WITH THE STAGES OF THE OESTRAL CYCLE

In their work on the histology of the anterior hypophysis of the female rat, Wolfe and Cleveland found cyclic histological changes in the anterior hypophysis of the rat which could definitely be correlated with the various phases of the oestral cycle. They found no evidence of quantitative changes in the relative percentages of cell types as correlated with the stage of the oestral cycle, but the qualitative or morphological changes in the cell types, as correlated with the different periods of the oestral cycle, were striking and constant.

3. Data on this group of animals are not presented in this paper but will be given in a later and more comprehensive paper on cyclic histological changes in the anterior hypophysis of the rat.

In the anterior pituitaries of animals killed in prooestrus, both large and small (with intermediate variants) cells of type I (corresponding to the eosinophiles of the literature) were found. The small cells presented a narrow band of granular cytoplasm, immediately surrounding the nucleus, while the granular cytoplasm of the larger cells was more abundant. Both types stained intensely with orange G. The cell membrane was well delimited. These cells usually made up about 32 per cent of the total number.

The cells of type III (basophiles), ranging from 4 to 6 per cent of the total cells at this stage, were large, completely filled with granular material, and were heavily stained with aniline blue[4] (see Plate I, Figures 3 and 4[5]). A lesser percentage was seen with comparatively less granular material (Plate I, Figures 8, 9 and 10). In the cells of type III a clear area called the macula by Addison (1917) and Rasmussen (1921) was observed. This is supposedly the area of the Golgi apparatus; the colorless ring represents the negative image of the Golgi apparatus (Plate I, Figures 3 through 11).

The cells of type IV, comparable to the chromophobes of the literature, were usually described as nuclei surrounded by a few strands of pale blue-staining cytoplasm (Plate I, Figure 3). In some instances the cell membrane was definite; in others it was less easily identified. These cells, making up approximately 60 per cent of the cells present, showed comparatively little change in morphology in the various stages.

In hypophyses of animals killed in oestrus, both the large and small varieties of type I cells were packed with deep-staining granular material. The cells of type III showed a progressive reduction of granular material during the oestrus phase, so that in late oestrus, practically all of these cells appeared as large clear cells with light blue cytoplasm. A few contained small fragments of granular material stained a deep blue (Plate I, Figures 10, 11 and 12).

In metoestrus, the cells of type I were usually less closely packed with granular material and usually stained lightly with orange G. This was not invariably true but was more constant on the second day after oestrus. The cells of type III were essentially similar to those of late oestrus; that is, a few were found containing granular material, but more were found which did not contain granules. In the majority of these cells the cytoplasm was broken up and adherent to the nucleus. In most of these cells the macula was distinct. Often the cell membrane was indistinct (Plate I, Figures 10, 11 and 12).

In animals sacrificed during dioestrus, the hypophyses contained cells of type I which were of two varieties, fairly equally developed. The larger cells were loosely packed with granular material and stained less intensely with orange G. The smaller cells were packed with granules and stained intensely. The type III cells were equally divided between cells filled with granules which stained intensely and large, clear regressive forms which did not contain granules. (Compare Figure 3 with Figures 11 and 12, Plate I.)

From the above studies Wolfe and Cleveland concluded that there was a qualitative cyclic variation regarding the morphology of the granular cells which could be correlated with the various phases of the oestral cycle. This was most marked in the case of the cells of type III. The quantitative changes were not striking, as may be seen by reference to Chart I. A summary of the quantitative cell counts of Wolfe and Cleveland is reproduced both in Table 1 and Chart I.

THE ANTERIOR HYPOPHYSIS OF THE FEMALE RAT AFTER CASTRATION

The Hypophyses of Female Rats Castrated for 5 Days. Fourteen female rats were sacrificed 5 days after the removal of their ovaries. The sizes of the experimental animals varied from 150 to 250 grams, and a cor-

4. Wolfe and Cleveland reported that another type of basophile cell was occasionally found in the anterior hypophysis of the rat. This cell contained well packed granules which stained a deep red or purple-red. It was quite similar to the cells of type II (one of the two basophilic types) found in the anterior hypophysis of the dog. The number of such cells in the pituitary of the rat was never great enough to be calculated in terms of percentage.

5. In their paper on the cyclic histological changes in the anterior hypophysis of the rat, Wolfe and Cleveland failed to publish photomicrographs of the cells described. For that reason, photomicrographs of basophile cells of normal female rats are included in this paper.

TABLE 1

SUMMARY OF QUANTITATIVE DATA

In the various columns the arithmetic mean, together with the probable error (calculated from the standard deviation) is given.

Type of Animal	Number of Animals	Body Weight, Gms.	Hypophysis Weight, Mgm.	Factor	Relative Percentage of Cell Types Present					Cells Counted
					Type I	Type III	Castration Cells	Type III + Castration Cells	Type IV	
Prooestrus	6	.....	.....	.....	32.7±2.6	5.0±0.4	.....	.....	62.6±4.3	.6.525
Oestrus	11	.....	.....	.....	31.8±2.5	6.1±0.8	.....	.....	61.2±2.1	36,054
Metroestrus	11	.....	.....	.....	33.5±1.5	3.9±0.6	.....	.....	62.0±2.1	33,120
Dioestrus	12	.....	.....	.....	31.0±2.5	4.6±0.9	.....	.....	65.0±2.9	33,699
Mean					31.8±3.1	4.6±0.9			62.4±3.5	
5-Day	18	200±17.6	7.6±0.9	3.7±0.4	32.7±1.0	6.4±0.7	.....	.....	60.6±2.5	38,889
10-Day	8	177±18.2	7.5± 0.9	4.0±0.1	35.5±1.6	8.6±0.9	.....	.....	55.3±3.3	20,108
15-Day	10	204±23.4	7.8±1.3	3.8±0.2	34.6±1.1	9.2±1.0	.....	.....	54.6±1.3	30,127
30-Day	8	181±14.3	6.2±0.5	3.7±0.2	38.2±2.6	12.3±0.6	.....	.....	49.2±1.8	19,233
30-Day	13	213±18.8	8.9±0.6	4.3±0.3	42.8±1.9	14.2±1.1	0.9±0.2	14.5±1.4	41.2±1.6	40,281
60-Day	14	241±18.7	9.8±0.7	4.1±0.3	42.4±2.8	12.8±1.5	4.1±0.8	16.9±2.0	39.7±2.6	44,281
90-Day	11	281±20.0	11.8±0.9	4.3±0.3	38.0±0.7	8.8±2.1	9.5±1.1	18.4±1.5	43.0±0.8	26,480
120-Day	9	294±19.9	12.3±0.5	4.3±0.5	40.8±4.0	6.4±1.1	11.3±1.5	17.6±1.7	41.8±2.1	28,713
180-Day	9	298±43.3	13.0±1.3	4.3±0.4	36.5±2.5	8.2±1.5	13.0±2.1	20.3±3.7	42.5±3.9	27,689
237-Day	2	Adults	.....	.....	35.0±5.2	5.0±0.5	11.0±1.2	16.0±0.7	50.0±3.4	5,300
590-Day	2	Adults	.....	.....	38.0±2.6	3.0±0.5	11.9±0.5	15.0±0.8	46.0±1.2	5,300
Total Castrates	100									286,218
Total Normal	40									119,398

responding weight of the hypophyses showed a rather constant factor denoting the relation between pituitary and body weight. These factors varied from 3.3 to 5.0 with a mean of 3.7 (see Table I).

The relative percentage of cells of type I (eosinophiles) in the individual glands studied showed a variation[6] of approximately 15 per cent in case of the chromophobes and eosinophiles, but only 4.7 per cent in the case of the basophiles (Chart I). This was the widest variation of percentages that we encountered in the entire study. The cells of type I, with a mean of 32.7 per cent, were essentially the same as described for the normal female. The cells were filled with well-stained granular material and most closely resembled those found in the oestral stage of the normal cycle. No cells were seen showing loss of granular material. There was no definite increase in size of the eosinophilic cells. At this level, measurements of these cells averaged about 8x8 micra, with most of the variations lying between 6 and 10 micra. The type I cells were fairly uniformly scattered throughout the anterior lobe, being only slightly increased centrally (see text figure 1).

The average percentage of the cells of type III (basophiles) was 6.3, which was near the upper limit of normal for non-castrated females. A majority of the cells of type III exhibited granular loss (Plate I, Figures 8, 9, 10, 11 and 12). In many of these cells, a macula and negative image of the Golgi apparatus were observed, although it was faint in some instances (Plate I, Figures 10 and 11). Such cells were most abundant in the central parts of the two lateral areas of horizontal sections (text figure 1). A lesser number of the cells of type III failed to show marked granular loss (Plate I, Figures 4 and 5). In such cells the macula was quite evident. Several of the pituitaries from 5-day castrates presented a histological picture similar to a dioestral type of gland; others were more similar to the oestral type (those in which all the cells of type III exhibited granular loss). The cells of type III found in these glands (both those packed with granules and those which exhibited granular loss) were similar in size and morphology to the basophilic elements of anterior lobes from normal animals. It should be emphasized that these cells exhibited much more granular loss than was found in animals which had been castrated for longer periods. Near the periphery of the section the cells of type III usually contained more granular material than those in the center of the section. In the posterior region of the section, next the residual cleft, many small granular cells of type III (Plate I, Figure 3) were seen (text figure 1, area designated by X). These had the typical morphology of the large type III cell (Figures 4 through 6) except that the granular material was finer and more diffuse. The periphery of the gland showed a predominance of cells of type IV, and as will be

6. In making quantitative studies on the cell types of the anterior hypophysis, variations in the levels of the various cell types present in the pituitaries of rats killed under apparently similar conditions are invariably found. In this paper it is seen that such variations are present; however, they are never so great as to invalidate the finding that there are progressive quantitative changes in the various cell types following ovary removal in female rats. However, such variations among individual animals make the use of a considerable number of animals in each group necessary.

pointed out later, many new cells of type III were found in this area in animals which had been castrated for longer periods. The type IV cells were normal.

There were very few changes in the general vascularity of the gland but peripherally a few dilated capillaries were seen; cells of type IV were predominant. The cleft contained colloid in only two of the fourteen glands studied. In those two the colloid stained red and formed a crescent between the intermediate and anterior lobes.

The Hypophyses of Female Rats Castrated for 10 Days. Eight female rats were sacrificed on the tenth day following castration. It is shown in Table 1 that the variations in weight of the animals and pituitaries were not markedly different from those removed at five days. That there has been very little gross change in weight is well indicated by a factor of 4.0 as against 3.7 of the five-day castrates.

The cells of type I showed a slight mean increase, as is seen in Table 1 and Chart I, but the range of variation was practically the same as that found in the pituitaries of the five-day castrates and of normal females. Of more importance was the appreciable increase in size of many of these cells, especially those located in the central portion of the lateral areas of the anterior lobe (text figure 1). Here there were many which ranged from 8x8 micra to 10x10 micra, and there were only a few smaller than 8x8 micra. The granules appeared larger and were more easily identified. The staining was possibly a little lighter than in the five-day castrate cells. However, as the periphery was approached, a considerable number of small eosinophilic cells was seen which were not unlike those found in normal glands.

The type III cells of this level showed what we considered a progressive change from that of five-day castrates. There were present many more of the large basophilic cells which were located in the central part of the gland (text figure 1) which were either entirely devoid of granular material (Plate I, Figures 11 and 12) or contained a reduced amount of granular material (Plate I, Figure 9). There was, however, a small number of the small granular cells of type III (Plate I, Figure 3) among the large clear cells. Peripherally, there were many of the small granular cells of type III and some fairly large ones (10 to 15 micra). The mean percentage of the cells of type III was 8.6; the range was from 7.2 to 11.4. This represented a definite increase in the basophilic elements when compared with normals.

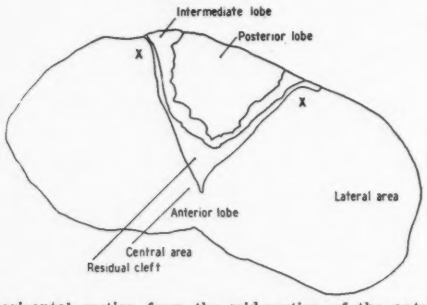
Coincident with the increase in granular cells, there was a rather definite decrease in the number of chromophobes. In two of the eight glands studied a small amount of colloid was found in the residual cleft. Mitotic figures were occasionally seen in this group (Plate I, Figures 2 and 3), as was the case in the five-day animals. These were not numerous but averaged about one figure per gland counted. These were chiefly found in the type IV cells but were found occasionally in type I cells that exhibited loss of granular material. They were never found in cells of type III. The

peripheral capillary dilatation was also more extensive in this group. See Chart I and Table 1 for quantitative data on this group of animals.

Female Rats Castrated for 15 Days. There were ten animals used in this series and the composite data are given in Chart I and Table 1. It is seen that the mean weight of the experimental animals is slightly higher than heretofore, but the pituitary factor of 3.8 indicates that there was no increase in the relative weights of the pituitaries in proportion to the average body weigh of the animal.

The average percentage of the cells of type I (eosinophiles) was practically the same as that found in the 10-day castrates. Reference to Table 1 and to Chart I will show that the range of variation was not great. In many instances the cells were larger and more intensely stained than those in the previous groups. The mean percentage of the cells of type III (basophiles) was definitely increased (9.4). A majority of those which were centrally located (text figure 1) were completely filled with granules. These

TEXT FIG. 1



A sketch of a horizontal section from the mid-portion of the anterior hypophysis of a female rat castrated for 60 days. The relationship of the several lobes is indicated and the hypophyseal cleft, which is distended by colloid, is seen crescented on the pars intermedia. Camera lucida drawing.

granular forms were quite large and were similar to the type III cells found in prooestrus (Plate I, Figure 4) but were possibly a little more intensely stained. The maculae in these cells were distinct. A considerable number of the cells of type III in this area exhibited loss of granules (Plate I, Figures 8 through 12). However, it was evident that such cells, showing reduction of granules, had materially decreased. This was, tentatively, interpreted as being the late stage of regression of the cells of type III, which were present at the time of castration. Peripherally, there were many more type III cells than were found in the 10-day castrates. They were quite large, ranging in size up to 16x16 mm., and were well-filled with granules which stained intensely (Plate I, Figure 5). However, there were also numerous small cells of type III present (Plate I, Figures 3 and 4).

Occasionally large granular cells of type III were observed which exhibited a number of very small vacuoles (Figure 13). Such cells often became filled with these tiny vacuoles, giving the cell a "spongy" appearance. These cells are described fully under the section dealing with the

pituitaries of 30-day castrates, because it was at this time that they first appeared in appreciable numbers. It seems that such changes in these large basophilic elements must be considered the first alteration, other than increase in size, which occurs in these basophilic cells after castration. Two of the ten glands showed colloid in the cleft.

The Hypophyses of Animals Castrated for 20 Days. The eight animals used in the group were castrated at known periods of the oestral cycle,[7] as can be seen by reference to Table 4. The factors of pituitary weight were the lowest of any of the groups studied; the mean was 3.7. The cells of type I were uniformly larger, and the granules were more closely packed and stained more intensely than did those in the pituitaries of 15-day castrates. The mean percentage, 38.2, was a moderate but definite increase over the mean of 31.8 per cent found in normal female rats; however, it must be emphasized that in 40 normal female rats these cells ranged from 21.9 to 41.1 per cent. In this normal tissue 9 glands had a level of type I cells between 25 and 30 per cent, 18 had a percentage between 30 and 35 per cent, and 9, a percentage between 35 and 40 per cent. In two glands the level of the cells of type I was below 25 per cent and in two it was above 40 per cent. It is seen, therefore, that, although the mean percentage of the type I cells in the pituitaries of 20-day castrates is higher than the mean found in normal females, the mean percentage of these cells found in the pituitaries of 20-day castrates was within the limit found in normal animals. As will be pointed out in the next section, castration in female rats does result in some increase in the level of the cells of type I. In 30-day castrates it was found that the cells of type I had a mean percentage of 42.8 per cent and in a majority of the individual glands the level of the cells of type I was above the normal limit of variation found in the pituitaries of normal female rats.

The type III cells (basophiles) had increased rather rapidly in percentage (a mean of 12.3, ranging from 10.6 to 16.7). In the central area there were many of the larger forms, measuring 16x16 mu. (Plate I, Figures 5 and 6). They contained intensely staining granular material and well defined maculae which were correspondingly increased in size.

On the periphery of the section the basophilic cells were very numerous, but were smaller than those centrally placed (Plate I, Figure 4). A few of the large cells of type III, exhibiting small vacuoles, were seen (Plate II, Figures 13 and 14). The cells of type IV were decreased and had a mean of 49.2 as compared to 62 per cent normally. Two glands showed colloid in the hypophyseal cleft. See Chart 1 and Table 1 for quantitative data on this group of animals.

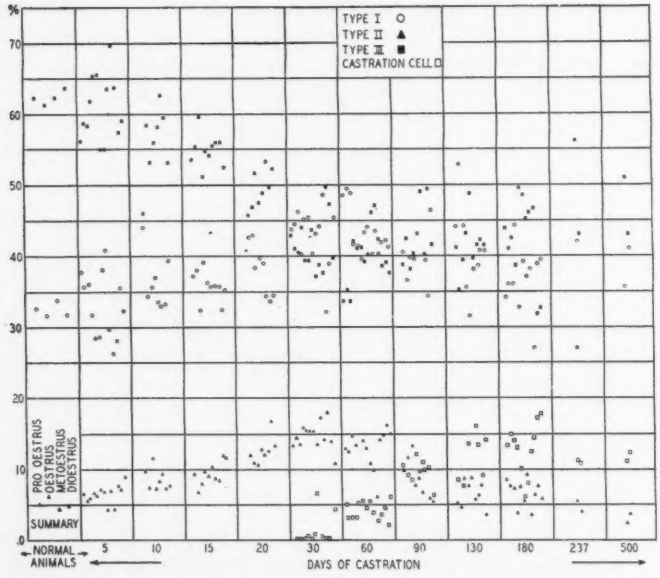
We were unable to correlate the histological picture presented in this group of animals with the phase of the oestral cycle in which the animals

7. These were preliminary experiments in which we were attempting to ascertain if the period of the oestrus cycle in which the ovaries were removed played any role in the later morphology of the pituitary. The data were inconclusive on these points. These experiments are being repeated. It seems possible that in such experiments the animals should be sacrificed at shorter intervals after castration.

were castrated. If the phase of the oestral cycle in which the animal is castrated plays a rôle in the subsequent histology of the anterior pituitary, it could not be determined in this group of animals, which had been castrated for 20 days. There is a possibility, however, that if we had studied these pituitaries at the end of a 5 or 10-day castration period, the pituitaries of animals castrated in the different periods of the oestral cycle might have varied.

Hypophyses of Female Rats Castrated for 30 Days. This group consisted of 13 female rats and, as can be seen by reference to Table 1, gave very consistent results as regards size of animals, hypophyseal factor and

CHART 1



Graphic representation of quantitative changes occuring after castration in the female rat, compared with normal female rats at the several stages of the oestrus cycle. The percentages of the several cell types are indicated on the ordinates. The normal females represent averages of 40 glands, while the castrate glands are separately charted. The periods of the oestral cycle and the length of time after castration are indicated on the abscissa. Cells of type I are indicated by open circles, type III cells by solid triangles, cells of type IV by solid squares and castration cells by open squares. The relative percentage of each cell type for individual groups in the case of the normal females and for each individual animal in the case of the castrated animals are in lines paralleling the ordinate (example: the mean percentages for prooestrus group are: cells of type I, 32.8; type III cells, 5; cells of type IV, 62.2). The open squares placed just on the abscissa represent fractional precentages or only occasional cells. See Tables 5 and 13.

relative percentage of cell types present. The factor of 4.3 was the largest yet encountered in the study, but is really only slightly above the earlier pituitary factors.

The percentages of the cells of type I were increased, the mean was 42.9. Their morphology varied as regards location. Near the periphery, where the type III cells were extremely abundant, the eosinophiles were fairly well divided between small and large varieties, and most of them

were filled with deeply staining granular material. Centrally, however, the cells were on the average larger, and a moderate number showed signs of granular loss; some of the cells were almost devoid of the deep yellow granules, while other showed a uniform distribution of large, light staining granules. There was no change in the nuclei of these cells and all showed distinct cell membranes.

The cells of type III were extremely abundant; the mean percentage was 14.2. This was the highest percentage of these cells observed at any time after castration. The central areas of the gland were fairly well saturated with these very large granular cells, but the peripheral portion contained more nearly a pure culture, especially anteriorly adjacent to the cleft (see area marked X in text figure 1). Here all sizes of this cell were found, ranging from the small cells seen in Figure 3 to the large cells seen in Figure 6 (see Plate I).

At this stage there appeared in appreciable numbers cells of type III (basophiles), which exhibited two distinctly new changes in morphology. The first change was the appearance of tiny spaces in very large basophiles (Plate 2, Figures 13, 14 and 15). A very few of the basophiles of the 15 and 20-day castrates showed these changes. A cell might contain either a very few or a great number of these small vacuoles. The appearance was distinctly "spongy." These small vacuoles did not contain blue-staining colloid such as that found in the large "signet ring" castration cells described below. The cells were either the extremely large ones as shown in Figure 14 or moderately enlarged cells like that shown in Figure 13. The granular content was moderately reduced and was in some cases apparently all gone, leaving a rather dense cytoplasm that appeared literally "packed full of holes." The macula and negative image of the Golgi body were well preserved in most of these cells. The multiple vacuoles seldom appeared to increase in size; however, in a few instances they did, and the result was the type of basophilic cell seen in Figure 15. It should be emphasized that these vacuoles were seldom as large as those pictured in Figure 15.

The second cytological change in the type III cells was the appearance of a few of the typical signet-ring castration cells which have been well described in the literature (Plate II, Figures 16 through 23; most of the castration cells found in this group of glands were the smaller variety). The castration cells were present in 11 of the 13 glands studied but in only four cases were enough present to make an appreciable count. These cells appeared first as moderately large type III cells with surprisingly large vacuoles which had pushed the nucleus and macula to one side, thus distorting the macula and less often the nucleus (Plate II, Figure 19). Such large castration cells were more abundant in later stages of castration. The very large vacuoles found in the castration cells at this stage usually contained light blue colloid-like material which is unfortunately not well shown in the photographs. Most of the castration cells found in these glands resembled those seen in Figures 16, 17 and 18, but usually had a more deeply

staining "colloidal" vacuole than is pictured except in Figures 16 and 20. Practically all these cells contained only a single colloid vacuole, which was extremely large. Confirming the view of many previous investigators, the castration cells are considered to be modified basophiles (our type III).

This latter type of cell was considered as the typical "signet-ring" type of castration cell. Such cells usually contained a macula near the periphery of the cell. The relation between the typical "signet-ring" type of castration cell and the "spongy" type of basophile as seen in Figures 13 and 14 was not clear. It might seem from superficial examination that the many small vacuoles found in the spongy type of basophile had coalesced to form a single large vacuole, thus producing a typical "signet-ring" castration cell. However, after careful and thorough examination of our material, we have become convinced that after a basophilic cell shows spongy changes, it seldom gives rise to "signet-ring" castration cells. We have rarely seen cells which might represent a transition between the large spongy basophiles with their many small vacuoles and the "signet-ring" castration cell. The writers believe that the "signet-ring" castration cells result as a modification of the basophiles which do not show spongy changes.

Reference to Table 5 and Chart I shows that the level of the type III cells (basophiles) reached a maximum (a mean of 14.6 per cent) in the pituitaries of the 30-day castrates and it is in these animals that the castration cells first appeared in appreciable numbers (a mean of 0.9 per cent). From this time through the later stages of castration, a reciprocal relationship between the type III cells (basophiles) and the castration cells was found. The castration cells increased in percentage in the later stages of castration, while the type III cells underwent a corresponding decrease. Reference to Table 1 will show that in the various groups of animals castrated from 30 to 500 days the total percentage of the type III cells plus that of the castration cells was always between 15 and 20 per cent.

In these 13 glands, 11 contained colloid in the cleft and one other, due to the absence of both posterior and intermediate lobes in the sections, was uncertain. The colloid in the clefts stained orange for the most part, but often showed a fading of the orange into a blue at one or the other end of the cleft. This blue colloid was not at all unlike that found in the castration cells. The cleft was lined with flattened epithelium.

Hypophyses of Animals Castrated for 60 Days. Fourteen female rats were used. The mean weight of the animals was slightly higher than in the previous groups; however, the factor, 4.1, found in this group, was closely similar to that found in previous groups.

The mean percentage of the cells of type I was increased to 42.4, slightly above that of the cells of type IV. This was the highest level of these cells found in the pituitaries of any of the castrated groups and was a definite increase over the level of these cells usually found in non-castrated rats. A majority of these cells were large and well-filled with well-stained granules.

The cells of type III and the castration cells were most interesting. Reference to Table 6 will show that there was a slight decrease in the number of the usual large granular type III cells and a definite increase in the percentage of castration cells (mean of 41.1, ranging from 2.3 to 6.2). The basophilic elements (type III cells) for the first time showed a decrease in relative percentage, falling from a mean of 14.2 to 12.8 per cent.

Two-thirds to three-fourths of the large granular type III cells exhibited many vacuoles (Figures 13 and 14). However, some still remain as typical large granular cells without any type of vacuolization (Plate I, Figure 6). The basophilic elements, as well as the castration cells, were very abundant throughout the entire section. All glands exhibited colloid in the residual cleft.

Hypophyses of Female Rats Castrated for 90 Days. Nine female rats weighing from 200 to 300 grams, with a pituitary factor of 4.3, were included in this group. The cells of type I were slightly decreased in mean percentage. A number of type I cells appeared regressive (exhibited granular loss), but a great number of cells did not appear to be involved.

The relative percentage of type III cells was definitely lowered, when compared with the 30- and 60-day castrates; from the high level at 30 days of 14.2 to 8.8 per cent. Approximately two-thirds of these cells were of the "spongy" type; many of the others showed evidence of granular loss similar to that found in the pituitaries of normal rats and early castrates (Figures 10, 11 and 12). In contrast, the "signet-ring" castration cells were definitely increased in percentage (mean of 9.5). Many were extremely large, often averaging 25x25 micra (Plate II, Figures 20 and 21). In some of these large castration cells a partial disappearance of the colloid from the large colloid-filled vacuole was observed; the result was a round "hole" left in the colloid-filled vacuoles of the castration cells. Such changes in these cells were interpreted as regressive changes in the castration cells. These changes are best understood by studying Figures 20, 21 and 23 in Plate II. We have, for the lack of a better term, called this regressive process "secondary vacuolization" of the castrate cell. Such secondary vacuolization was pronounced in this group of animals; probably one-fifth of all the castration cells showed such a picture as is represented in Figures 21 and 22, and a few showed late stages of regression as pictured in Figure 23 (see Plate II). See Chart 1 and Table 1 for quantitative data.

Hypophyses of Female Rats Castrated for 120 Days. The nine rats used had a mean body weight of 296 grams; the pituitary factor averaged 4.3. The level of the type I cells was about the same as that of the 90-day castrates. Most of these cells were medium-sized; they were well-filled with granules. Some exhibited granular loss. The percentage of type III cells was further decreased; the mean was 6.5. Many of these were quite large and were filled with large, deeply staining granules. Only a few were of the "spongy" variety. The castration cells were increased in percentage (mean of 11.2) and were chiefly large types (Figures 18 through 23).

Many exhibited secondary vacuolization, as in the previous group (Plate II, Figures 21 through 23). The percentage of the type IV cells was about the same as in the previous two groups. Residual cleft colloid and the vascularity of the gland were essentially similar to the 60- and 90-day castrates; the other features of the histological picture remain unchanged. However, one could occasionally see blue material resembling the colloid in the castration cells, out in the extra-cellular spaces. See Chart 1 and Table 1 for quantitative data.

Hypophyses of Female Rats Castrated for 180 Days. This group of 11 animals, as may be seen by reference to Chart 1, had a mean body weight of 298 grams. The mean pituitary weight was 12.3, with a factor of 4.3.

The type I cells were very similar to those found in the hypophyses of 120-day animals. A few exhibited granular loss. The average percentage of these cells was decreased to 36.8, a moderate drop from the highest mean of 42.4, 120 days before (60-day castrates). The percentage of the cells of type III (basophiles) was low, namely, 8.2. Some of these cells were well-filled with granules (Figures 5 and 6); others were of the spongy variety (Figures 13 and 14). The percentage of castration cells (13.0) was slightly increased over that found in the 120-day castrates. Many were large, intact cells as seen in Figures 18, 19 and 20; others exhibited secondary vacuolization (Plate II, Figures 21, 22 and 23). The level of cells of type IV was practically unchanged; the mean was 42 per cent. For detailed quantitative data see Table 1 and Chart 1.

The vascularity was very little changed; possibly some decrease in the size of the centrally located channels had taken place. The residual clefts in all glands were packed with colloid, which in places could be seen to push out into the intercellular spaces, especially just below the hypophyseal cleft.

Hypophyses of Animals Castrated for 237 Days. Only two animals were available, due to the long time of experimentation and due to the late realization of the importance of long-term experiments. Unfortunately neither the animal nor the pituitaries were weighed, as at this time we had not obtained a torsion balance which facilitated rapid weights.

The cells of type I were variable, these being 27 per cent in one animal and 42 per cent in the other, so it is impossible to make an accurate statement concerning the level of these cells; they exhibited the same morphology as in the 180-day castrates. Of most interest was the low level of cells of type III in the pituitaries of both animals, which was about equal to the non-castrate animals. These cells were only moderately enlarged above the normal and were filled with deep-staining granules. Only a few "spongy" (Figures 13 and 14) forms were seen. A few exhibiting granular material were present (Figures 11 and 12). These cells of type III were, on the whole, much smaller than those found at 60 and 90 days after operation. The level of the castration cells was not increased over that found in the 180-day castrates, but those found were very large (Figure 20). The aver-

age percentage was 11 per cent for the castration cells and 4.9 per cent for the cells of type III (basophiles). See Table 1 and Chart 1 for quantitative data.

Since only two animals were present in this group, definite conclusions were not warranted. Probably the most striking feature was the low levels of cells of type III, which indicates that a definite regression does take place; the percentage of these cells tending to return to a level found in normal female rats. Study of the pituitaries of two female rats castrated for 500 days confirm this impression.

Hypophyses of Female Rats Castrated for 500 Days. The type I cells closely resembled those found in the pituitaries of non-castrated females; the mean was 38.6 per cent. The percentages of basophiles (our type III) filled with granules were extremely low, being only 3 per cent; most were of moderate size (Plate I, Figure 5). A few exhibited granular loss (Plate 2, Figures 10, 11 and 12). The castration cells were found to be at a high level (11.9) and were quite large (Figures 20 and 21). Many showed secondary vacuolization (Figures 21, 22 and 23). Many were extremely regressive (Figure 23). See Table 1 and Chart 1 for quantitative data.

DISCUSSION

Examination of the literature reveals the fact that the most constantly reported effect of castration on the anterior hypophysis of the rat has been an increase in the number and size of the basophilic cells and their alteration into the castration cell type. Our results fully confirm this view. However, our studies have also revealed that there is a more or less orderly and constant sequence of morphological and quantitative changes occurring after castration and that the time factor is of special importance in these changes. The studies presented in this paper indicate that there was a progressive increase in the number and size of the basophilic elements, reaching a maximum (14.2 per cent) on the 30th day after castration. During the early days of castration (5, 10 and 15 days) many of these cells exhibited granular loss. After that time, however, a majority of the type III cells were extremely large and packed with granules. Castration cells were found in appreciable numbers in 30-day castrates. From this time the castration cells progressively increased in number and in animals castrated for 180 days the mean percentage of these cells was 13.0. In animals castrated for longer periods there was little change from this high level. From the 30th day of castration there was a gradual decrease in the level of the cells of type III (basophiles); in animals castrated for 180 days the mean percentage was 8.2, and in animals castrated for 500 days the average percentage was only 3.0. This last figure represented a drop of approximately 11 per cent from the high level of 14.6 per cent found in 30-day castrates. (During the same period there was an increase of the castration cells from 0.9 per cent in 30-day castrates to 12.7 per cent on the

PLATE I

All figures in Plates 1 and 2 are photomicrographs with a magnification 1660 times, using a G filter.

Figure 1. A cell of type IV (chromophobe) centrally placed in the photograph shows a prophase mitotic figure (taken from pituitary of a female rat castrated for 30 days).

Figure 2. A cell of type IV (chromophobe) showing a telophase mitotic figure (taken from pituitary of a female rat castrated for 60 days).

Figure 3. A small cell of type III (basophile), well filled with granular material, is seen surrounded by several non-granular cells of type IV (chromophobes).

Figure 4. A normal or average-sized type III cell (basophile), well filled with granular material and showing a well defined nucleus and macula. Figures 3 and 4 represent granular type III cells found in normal female rats.

Figure 5. A large type III cell (basophile), well filled for the most part with granular material as found in hypophyses of castrated female rats.

Figure 6. A second large type III cell (basophile) filled with large granules which stain intensely with aniline blue, characteristic of the pituitaries of female castrated rats.

Figure 7. A type III cell (basophile), showing beginning granular loss in the upper left part of the cell. Small clear areas are also seen in the superior part of the cell and some clumping of the granules is seen at the lower pole of the cell.

Figure 8. Two type III cells (basophiles), showing clumping of granular material into deeply staining masses. Found in both normal and castrated female rats.

Figure 9. A cell of type III (basophile) frequently seen in normal and early castration hypophyses. A marked reduction in granular material is present. The cytoplasm is fragmented and most of the granular material present is in small clumps.

Figure 10. A cell of type III (basophile) that contains very small amounts of granular material clumped near periphery of cell. A faint image of macula is seen to right of nucleus.

Figure 11. A large clear type III cell (basophile) showing total granular loss. The cytoplasm is stained light blue but large clear areas are seen. The nucleus is well outlined and a faint outline can be seen of the macula. The cell membrane is indistinct. Such cells are characteristic of normal rats killed in oestrus and during the early periods of castration.

Figure 12. A small clear blue cell of type III (basophile) containing no granular material and sparse blue cytoplasm. The cell membrane is indistinct.

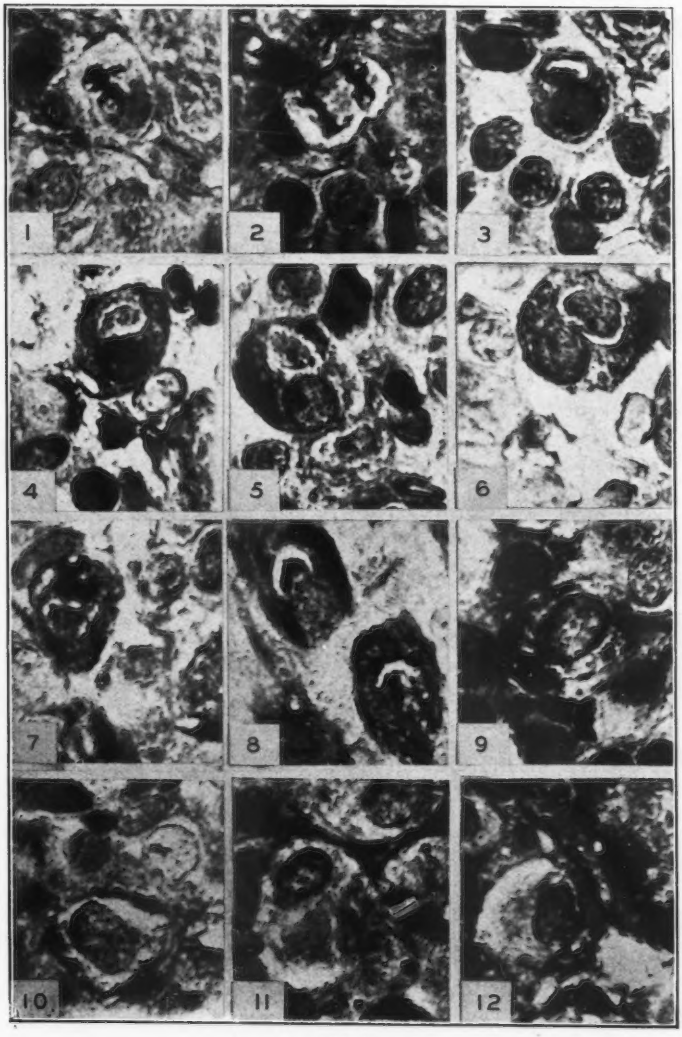


Plate I

PLATE II

Figure 13. A large type III cell (basophile) containing many minute clear areas or vacuolated spaces is observed. A well defined macula is present and a less well defined nucleus is seen at the lower pole of the cell. Found chiefly in hypophyses of animals castrated from 30 to 90 days.

Figure 14. A large type III cell (basophile) showing more diffuse clear areas with a typical "spongy" effect typical of a large percentage of the type III cells in hypophyses from animals castrated for 30 to 90 days.

Figure 15. A cell of type III is exhibited containing various sized clear areas or vacuoles in the cytoplasm. This type of basophile is infrequently observed; this is from an hypophysis from a female rat castrated for 30 days.

Figure 16. This cell is a small castration cell containing a blue-grey colloid vacuole and fine granular cytoplasm. Such castration cells as this and figures 18 to 20 inclusive are typically found in hypophyses of animals castrated for 30 to 180 days.

Figure 17. This castration cell is a larger, deeply staining granular cell with a moderate sized colloid filled vacuole, characteristic of pituitaries of rats castrated for 30 days or more.

Figure 18. This photomicrograph presents a typical large "signet-ring" castration cell with the cytoplasm, macula and nucleus pushed to one side by the large, clear, colloid-filled vacuole.

Figure 19. Two large typical castration cells are observed, typically found in hypophyses from animals after 60 days of castration.

Figure 20. The cell represents the largest castration cell observed.

Figure 21. This large castration cell contains a round clear area in upper left portion of the colloid-filled vacuole; such cells as this and those represented in Figs. 21 to 23, inclusive, are found in the late stages of castration (after 90 days).

Figure 22. This castration cell contains two secondary clear areas or vacuoles in the colloid vacuole.

Figure 23. This cell represents a degenerate stage of a large castration cell. Several clear areas are seen, completly replacing the vacuole, and the cytoplasm has been fragmented, and shows signs of dissolution. This represents a late degenerate change in a castration cell.

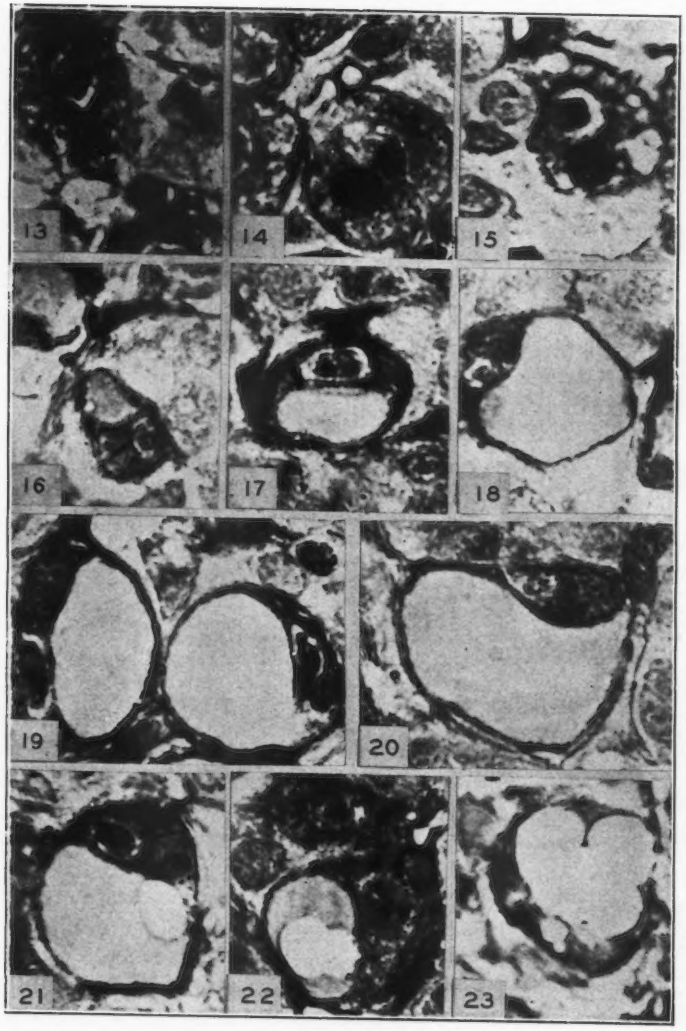


Plate II

180th day.) Our studies indicated that the castration cells were modified basophilic elements, confirming the view of previous investigators.

The changes in the basophilic cells after castration are fairly constant and the conclusion that they are definitely increased in number and size is fully justified. However, the possible changes in the eosinophiles (our type I) are not so easy of analysis and it is felt that definite conclusions are not justified at this time. Our studies on 40 normal female rats, killed at various phases of the oestral cycle, indicate that the level of the eosinophiles in these animals is most often between 30 and 35 per cent. The average was 32.8 and the arithmetic mean was 31.8, with a probable error of ± 3.1. However, the level of these cells in a few instances ranged up to 40 per cent or slightly above. In our 30- and 60-day castration groups, practically all the rats (25 out of 27) presented a level of eosinophiles of 40 per cent or above. The arithmetic means were 42.8 ± 1.9 and 42.4 ± 2.8, respectively. Thus, comparison of this group of castrated rats with the normals would indicate that in our 30- and 60-day castrates there was some increase in the numbers of the eosinophilic cells. However, this high level did not persist in the long term castrates and it is possible that if more pituitaries had been analyzed that our results concerning the increase in the number of eosinophiles after castration might have been altered.

Mitoses (Figures 1 and 2) were found in about one-third of the glands studied, but never more than two or three in the sections of any one gland. They were found for the most part in the cells of type IV (chromophobes) but occasionally they were found in cells of type I (eosinophiles) which exhibited loss of granules. No mitotic figures were found in the cells of type III (basophiles).

SUMMARY

1. Studies were made on the pituitaries of 100 female rats from which the ovaries had been removed at various intervals (5-500 days) before they were sacrificed. The work was controlled by observations on 40 normal female rats.

2. It appeared that there is a quantitative increase in the percentage of the cells of type III (basophiles) until about the 30th day of castration. The mean percentage of these cells in 30-day castrates was 14.2 as compared with 4.6 for normal non-castrated females. From the 30th day of castration there is a gradual decrease in the percentage of the basophilic elements.

3. In the early periods of castration (5 to 15 days) the cells of type III often exhibit granular loss. After this time, however, they rapidly increase in size and become packed with granules which stain a deep blue with aniline blue. At about the 30th day of castration, large colloid vacuoles appear in these cells and they give rise to typical "signet-ring" castration cells.

4. In animals castrated for 30 days, the percentage of the castration cells is low (0.9 per cent). From this time they increase rapidly in number

and in animals castrated for 180 days the mean percentage was 13.0 per cent. During the same period the percentage of the type III cells decreased.

5. There is a moderate increase in the percentage of the cells of type I (eosinophiles) during the first 60 days of castration. Later, they tend to decrease in number.

6. There is no morphological change in the cells of type IV (chromophobes) after castration.

7. Colloid accumulates in the residual cleft following removal of the ovaries.

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COMPARATIVE SENSITIVENESS OF SCHIZOPHRENIC AND NORMAL SUBJECTS TO GLYCERIN EXTRACT OF ADRENAL CORTEX

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Four decades ago the effectiveness of a glycerin extract of adrenal gland was described in the publications of Oliver and Schäfer (1). During the interim a similar extract of adrenal cortical material has been manufactured by a commercial firm as a stock preparation and two years ago it was brought to our attention as a potentially valuable medicament in the treatment of schizophrenia.* In previous publications (2) (3) we have discussed some effects arising from the oral administration of this substance as determined in schizophrenic subjects. Whether similar results would be obtained in normal individuals was explicitly left as an open question. This communication deals with a study devoted to an attack on that particular problem.

As the outstanding property of the cortical material is its stimulating effect upon the blood pressure, it was decided at this juncture to investigate that feature alone. As the optimal daily dosage in the patients seemed to be 45 pills, representing 450 grains of adrenal cortical substance, this same amount was administered to eight normal subjects. Blood pressure readings were taken three afternoons of each week after thirty minutes' rest in bed. For the purpose of establishing a base line, the subjects were studied for one week without medication, following which the cortical material was administered for a two-week period.

The results of the investigation are shown in Figure 1, in which is depicted the change in the systolic blood pressure from the premedication level to that after two weeks of medication in both normal and schizophrenic subjects, each bar representing a different individual. The data on the patients are taken from the previous study (3). If we may assume a normal variation within plus or minus 5 mm. in the systolic blood pressure under comparable resting conditions, it is seen that of the normal subjects two individuals had a pressor effect and one a depressor effect beyond these limits. On the other hand, in the case of the patients one individual showed no change while the other nine showed a rise in systolic blood pressure of more than 5 mm. Not only was the incidence of the pressor effect much higher in the patients, but also the magnitude of the reaction was greater, the maximum rise of 13 mm. in one normal subject being equalled by two patients and surpassed by four others. This difference in reactivity is

*We are indebted to Schieffelin & Company of New York for generous supplies of the extract.

reflected in the fact that the mean rise in the systolic blood pressure of the patients was 17 mm. as compared with 2.6 mm. in the control subjects. Comparable differences were found between the normal and the psychotic subjects as regards the diastolic pressure.

Although the reactivity of the patients was definitely greater in the two weeks' period, the possibility arose of a mere delay in the pressor reaction on the part of the normal subjects. Accordingly, it was decided to repeat the experiment over a longer period of time. A fresh supply of the cortical extract was obtained and a study was made of the blood pressure reaction in two new groups of ten healthy schizophrenic and ten non-psychotic individuals, the latter chosen from the staff and employees of the

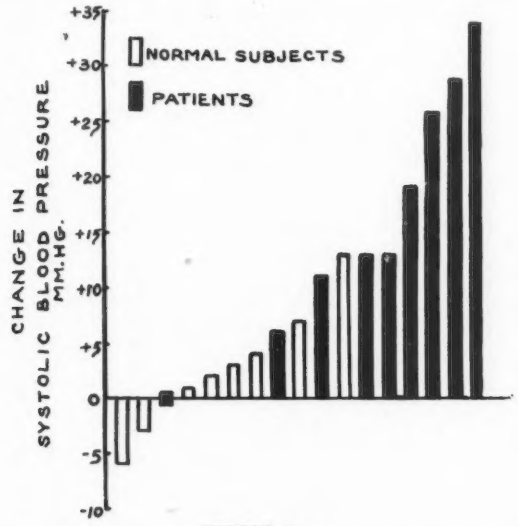

FIGURE 1

Change in systolic blood pressure after two weeks' administration of the adrenal cortex preparation to 8 normal controls and 9 schizophrenic patients. Each bar represents a different individual. The subjects are ranked in the order of their reaction to the cortical substance, a plus deviation designating an increase in blood pressure and a minus deviation designating a decrease.

Worcester State Hospital. Of the normal group, nine were presumably free from organic disease and the tenth had a mild vasomotor neurosis of the Raynaud type. The blood pressure readings were obtained in the afternoon four to five times each week after 30 minutes' rest in bed. Studies during an initial week without medication served to establish control levels. Following this, all the subjects were started on the same day on the cortical extract, on the same dosage of 45 pills daily, the experiment being continued over a four-week period of medication. The individual reactions of the systolic blood pressures of the subjects are shown in Figure 2, in which each bar represents in a different individual the change in blood pressure from the initial levels to those obtained during the fourth week of medica-

tion. During this interval the variation in the systolic blood pressure was at times irregular, there being an occasional rise in the normal individuals in the first weeks of medication. This was not sustained, however. In the patients in whom a pressor effect was visible, it was generally consistently maintained.

The distributions of the pressor reactions are essentially similar to those in Figure 1. Among the normal subjects, a rise of 14 mm. in systolic blood pressure was observed in the individual with Raynaud's disease. Of the other nine in whom presumably no organic disease was present, only one showed an elevation in blood pressure greater than the normal limits of variation and this was only 6 mm. Of the patients, seven of the ten displayed a pressor effect of more than 5 mm. Thus, it would seem from this longer study that the pressor reaction in most of the normal individuals

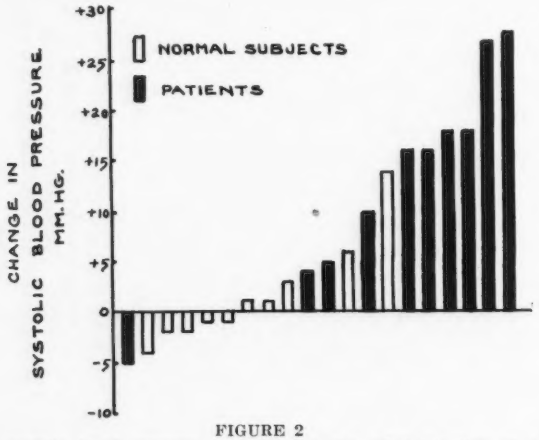

FIGURE 2

Change in systolic blood pressure after four weeks' administration of adrenal cortex extract to 10 normal controls and 10 schizophrenic patients. Each bar represents a different individual. The subjects are ranked in the order of their reaction to the cortical substance, a plus deviation designating an increase in blood pressure and a minus deviation designating a decrease.

was not merely delayed but was actually absent. Combining the two series of organically healthy individuals we find that a pressor reaction was present in 79 per cent of nineteen schizophrenic patients as compared with 18 per cent of seventeen normal subjects.

The individual responses in the diastolic pressures are not reproduced since the results were essentially similar to those of the systolic blood pressures except that in four of the normal individuals, including the one with Raynaud's disease, a rise of 6-9 mm. was observed during the four weeks of medication. Apparently the cortical substance may provide some stimulus to this phase of blood pressure even though the systolic component may not present any evidence of it.

The reactions of the two groups in the second series are portrayed in Figures 3 and 4. In regard to the systolic pressure, it is seen that the

patients' curve rises steadily upwards while that of the nine normal individuals (the subject with Raynaud's disease was excluded) remains essentially unchanged. It is, of course, true that in mass trends of this type, individual irregularities are submerged and the curves may be somewhat deceptively smooth. In the diastolic pressure of the patients a trend similar to that of the systolic pressure is evident, while in the normal subjects a slight degree of stimulation seems to be present.

In the second series the mean systolic blood pressure of the normal subjects in the control week was 111.3 mm. and during the fourth week of medication remained at 111.2 mm. The mean diastolic blood pressure of the control individuals began at a level of 67.1 mm. and during the experi-

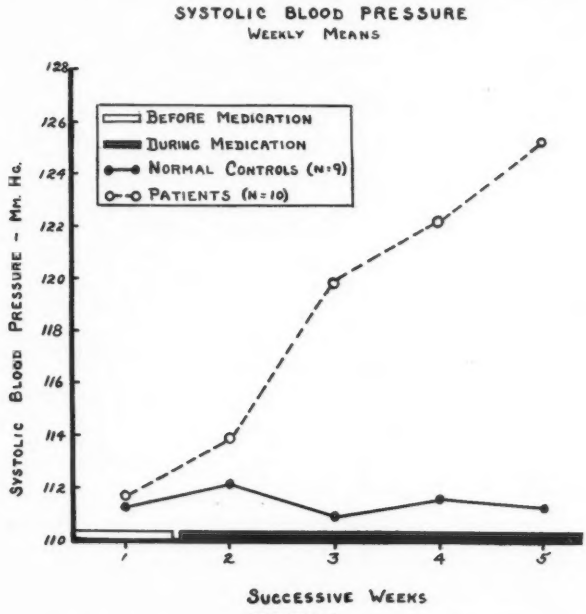

FIGURE 3

Weekly group means of systolic blood pressure in 10 schizophrenic and 9 normal subjects after the administration of adrenal cortex extract.

mental period rose slightly to 70.8 mm. In the patients, the mean systolic blood pressure in the initial week was at the same level as that of the normal subjects—111.7 mm.—but during the final week rose to 125.3 mm. The mean diastolic blood pressure of the patients during the control period was 66.5 mm. and during the fourth week of medication increased to 78.5 mm. Statistical analysis of the data by the method of Fisher's "t" (4) shows that the changes in systolic and diastolic blood pressures in the patients are statistically significant and beyond the possibility of chance variation while in the normal subjects such changes as are evident are not significant.

DISCUSSION

Few data are available to throw light on the reason for this difference in reaction between the normal and schizophrenic subjects. It is not dependent on any difference in the level of blood pressure between the two groups for in each the means and the distributions of the initial readings were essentially the same. In age the two groups were quite similar. It is unlikely that hospitalization in the case of the patients would predetermine a pressor reaction to the material—especially in view of the fact that the duration of hospitalization bore no relationship to the height of the pressor reaction. The supposition that the patients were suffering from adrenal deficiency

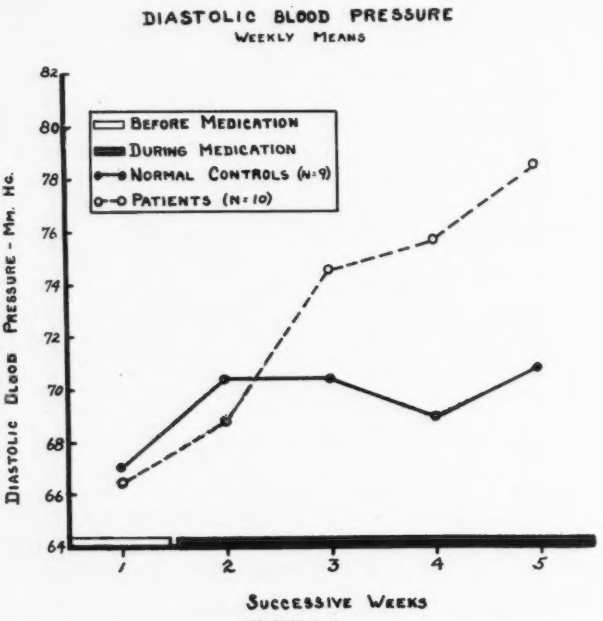

FIGURE 4

Weekly group means of diastolic blood pressure in 10 schizophrenic and 9 normal subjects after the administration of adrenal cortex extract.

seems worthy of consideration. It is a common belief among experienced clinicians that deficiency of a given hormone renders the subject more reactive to it. Collip has recently propounded this as a principle of "inverse response" (5).

The general metabolic picture seen in schizophrenia is such as, independently, to suggest adrenal deficiency. Indeed it was the recognition of this possibility that first led us to an empirical test of cortical extract as a therapeutic agent. The low basal blood pressure (6), the diminished oxygen consumption rate (7), the tendency to anaemia (8), and sub-normal body weight (8) that are seen in the psychosis have all been noted as character-

istic of such deficiency in man. Animal experimentation supplies other analogies. Adrenalectomized animals prior to the onset of more severe symptoms exhibit increased urinary output (9). Similarly, our patients have been found to have a urinary output twice that of normal individuals living in the same environment (8). Hartmann, Lockwood, and Lockie (10) have shown that adrenalectomy renders rats less resistant to heat. Likewise, Gottlieb and Linder (11) have found that after exposure to moderately high environmental temperatures there is a greater rise in the body temperature of schizophrenic patients than in normal subjects.

These findings raise several questions that demand further study. To what extent and how consistently does adrenal deficiency figure in the schizophrenic picture? Is the deficiency—if it actually exists—a cause, effect, or concomitant of the psychosis? With more accurate grading of dosage could the pressor reaction be used as a pathognomonic diagnostic criterion between the schizophrenic and the normal subject? Is the reactivity shared by other types of psychotics? In any case, what is the mechanism underlying the exaggerated reaction to cortical extract that is seen in the schizophrenic? What is the practical therapeutic value of the extract we are using? These problems are under further investigation.

SUMMARY

1. A glycerin extract of adrenal cortex was administered to healthy male schizophrenic and to normal subjects in a daily dosage representing approximately 450 grains of cortical substance.

2. In a first series of subjects in which the medication was administered for two weeks, two of eight normal controls and eight of nine patients showed a pressor reaction.

3. In the second series in which the medication was administered for four weeks, one of nine normal controls and seven of ten patients showed a pressor response.

4. Combining the two series, 18 per cent of the normal subjects as compared with 79 per cent of the shizophrenic patients showed a pressor reaction.

5. In the first series of patients the mean rise in systolic pressure for the group was 17 mm., a statistically significant change.

6. In the first series of normal subjects the mean rise in the systolic pressure for the group was 2.6 mm., an insignificant variation.

7. In the second series of patients the mean rise in systolic pressure for the group was 13.6 mm. and for the diastolic pressure 12.02 mm., these changes being statistically significant.

8. In the second series of normal subjects, there was no change in the systolic blood pressure of the group. The mean diastolic blood pressure rose 3.73 mm., an insignificant variation.

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THE PSYCHOLOGICAL PICTURE OF A CASE OF LAURENCE-MOON-BIEDL SYNDROME

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Although mental deficiency is one of the cardinal symptoms of the cerebral adiposity syndrome described originally by Moon and Laurence and subsequently Biedl, most of the case reports have only mentioned its absence or presence. Few have described the mental picture more than to state that the patient was "retarded" or "demented" or "imbecilic" and only six cases have given the results of a psychometric examination. No reports have described the mental picture in any detail.

No attempt is made here to review the literature. Ornsteen has summarized the pathogenesis and heredity and Reilly and Lisser have contributed a very excellent survey of all the reported cases up to their time of publication (1932) with the addition of four cases of their own, a total of 77 cases. They list the six cardinal symptoms as obesity, genital dystrophy, retinitis pigmentosa, mental deficiency, polydactylism, and familial occurrence. Of the 77 reported cases, 25 showed the complete set of symptoms and 10 were questionably complete. Twenty-six cases showed five of the six symptoms, with either retinitis or polydactylism.

Of the 77 cases reviewed by Reilly and Lisser, 60 showed mental deficiency 7 did not, and in 11 it was not stated. The intelligence quotients are given in six instances, varying from 22 to 50 per cent. These writers also review the results of treatment; in seven reports the authors failed to note any improvement with various forms of opotherapy. Many writers report some improvement, most commonly, in the obesity and next most commonly in an improvement of the mental retardation. Six writers report improvement in the mental condition in nine cases, using various combinations of thyroid, pituitary, and ovarian extracts. In Turner's case, the I. Q. is said to have improved from 50 to 76 per cent within a year.

The present study concerns a boy, age 18, one of identical twins, showing obesity, genital dystrophy, mental retardation, retinitis pigmentosa, and the same findings in the twin brother except there was no retinitis. The patient was observed and treated in the hospital over a period of three months and there has been an opportunity for several follow-up contacts with him.

The psychological picture in this case not only details the "mental retardation" of the Laurence-Moon-Biedl syndrome, but is characteristic of the clinical picture so often associated with the typical hypopituitary adiposogenital dystrophy. In a previous study of the mental disturbances associated with pituitary disorders, several instances in the literature were cited and some cases given to illustrate the frequent association of either

mental retardation or emotional instability in the typical Frölich syndrome. The present case shows not only the intellectual retardation, but also the effect of training and environment on the emotional strivings as they are reflected in his attempts to compensate for the physical and mental handicap.

CASE REPORT

Statement of the Problem. A school boy aged 18 was admitted to the hospital because of many minor behavior problems, falsification, running off from school, inability to get along with people, and backwardness in his academic work.

Family Background. The paternal grandfather died at 74 years of age from "bladder trouble"; he never got along with his children and manifested little interest in them; he is described as "niggardly." The paternal grandmother is living and in fair health; she is described as an easy-going, ambitious individual. The maternal grandfather committed suicide supposedly because of financial difficulty; the maternal grandmother is living and in good health. She is a domineering, selfish individual expecting her children to drop whatever they are doing at her request, though she has always been generous towards them.

The patient's father, a stern, serious, "all business" man, is 46 years old, is in good health and has normal weight for his height. He operates a series of chain stores and has always been very active socially in the community. His chief interest in the patient's difficulty was to determine the chances of his son to become a useful citizen; he was concerned in trying to ascertain if the boy is likely to commit some crime, how much and what type of education may be advisable or suitable and what sort of occupation he might be able to follow.

The mother is 41 years old and is in good health, but has had many chronic complaints. She was treated at a large clinic eight years ago but no organic difficulty was found. She is of medium height and build. She occassionally becomes dramatic in her conversation, often with much show of emotion. She speaks of the children as very "adorable boys," still referring to them as her "little boys," though all three children are much heavier and taller than she is. She regarded her children as bright even though they were late in learning to speak and behind their grade in school. She sacrificed her whole time during their childhood to work and play with them. With much emotion, she frequently defends the boys' behavior though undoubtedly is defending herself. She is socially inclined and has often opened her home to parties for the young people, who "usually tear the house to pieces." She shows much less emotion about the youngest son in contrast to the twins. She herself is a twin, the other being a brother who caused her parents much grief by his lack of ambition and waywardness.

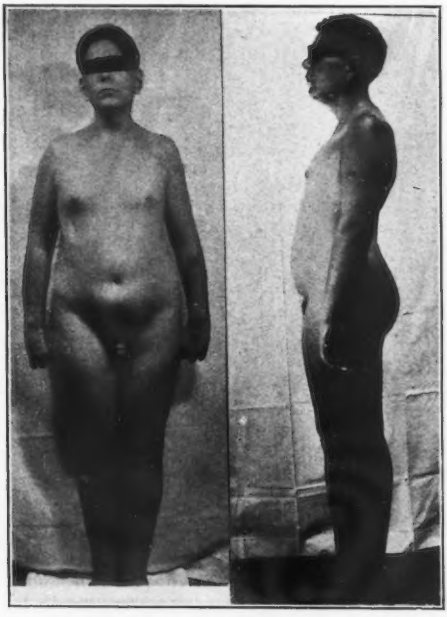
Neither of the parents has fully appreciated the significance nor the extent of the illness of the patient nor his twin brother. As in most similar situations the mental retardation was defended, excused and rationalized.

Developmental History and Illness. The mother was 23 when the identical twins were born. She was ill throughout the pregnancy, being confined to bed much of the time. The children weighed 4½ pounds each and gained slowly to weigh 16 pounds at the end of their first year. They sat up from the sixth to eighth months and learned to walk by the fifteenth month. There was much feeding difficulty with artificial food and resultant colic and crying. The patient had an umbilical hernia which closed without operation during the second year. They were weak, awkward, and used their hands clumsily. They did not talk until after a year of special training, at a school for the deaf, at the age of four. Apparently they both could hear and learned after a period of a year to talk. At about the age of 5 they were examined by a well-known pediatrician who said they were normal, according to the parents' story. Nevertheless medication was recommended and given for a time. The third child arrived at this time. The twins returned home and to school where learning proceeded very slowly, much of it being made possible only through the mother's help at home.

At the age of 9 they were examined at a clinic. The basal metabolic rate of the patient was minus 13, which was elevated to normal by thyroid. His I. Q. was 85; a diagnosis was made of Frölich's Syndrome. One of the twins then was given pituitary injections while the other served as a control and even at this time the patient put on many antisocial aggressive scenes against anyone who did not use solicitous maternal protection toward him. The pituitary treat-

ment was continued for a short time but because the twin became untruthful the medication was blamed and stopped.

The patient continued to get along with difficulty in school and usually slept late in the mornings and often fell asleep in various places during the day. He was a Boy Scout for two or three years but could not learn to tie the knots and so did not advance beyond the "tenderfoot" class. He was quite inactive physically, shunning all forms of active sport except swimming. In high school his difficulty increased; entering at 16 he was asked to join a fraternity. In order to go to the meetings at night it was necessary to promise his mother that he would come home in the afternoon to study, which he consistently did not do. He refused to drink with the members and to stay with one of them while he was sobering up. Finally on the charge of telling all the fraternity secrets to his mother he was tried and expelled. Later he was invited to join again but declined. He did not enjoy the parties because he could not find a girl and if he did he complained that she would "ditch him" for another boy. It was reported that more often he left the girl. Occasionally at parties at home he would go off to his room



Patient with Laurence-Moon-Biedl syndrome.

and read. Latin was difficult for him, but his mother explained this on the difficulty of articulation rather than comprehension. He often played truant from school and refused to stay for an extra period after hours to make up time. On another occasion when geometry was particularly difficult he ran away to the next town, where he gave a fictitious name to the officers, concocted a story of being deserted by his father, was given board at the County Farm, where he staged a "spell" of some kind in protest against enforced prohibitions. He frequently stole money from his parents, crying and showing great remorse when discovered, but failed to carry out the resolve not to do it again. His father tried to give the boy a regular weekly allowance, but this was spent all at once or without judgment. At home he was unhappy, particularly antagonistic against his father who, he said, "never had a pleasant word for him." The twins had very poor table manners, frequently spilling food, annoying and distressing the father, but being protected by the mother. The twins were spanked by the father, even up to the age of 17. Since then he has attempted to discipline them by scolding, depriving them of the use of the car, or other privileges.

The patient felt he did not have many friends, "just a lot of pretend-to-be friends." "They come to your home and mess things up," but they did not invite him to their parties. They did invite his twin, who has no difficulty in getting "dates," and who is regarded by the mother as being a Beau Brummel.

All three boys were sent to a Catholic school, our patient being 18 years of age. The one twin fitted in quite well with the program, was liked by the rest of the boys and, although sluggish in his studies, devoted himself to them. The patient was noisy, enjoyed arguing about anything, even with the teacher, and rather than be called a name he would take dares of the other boys to shout or throw things or blow a whistle in class. Because things were not running smoothly in the school the preceptor announced that any boy would be given money to go home who wanted to go. The patient went to him, obtained $15.00 and bought railroad tickets. When he attempted to cash a check his name was traced and his parents came for him. This episode preceded his admission to the hospital.

The patient had chicken pox at 12 months, mild pneumonia at 24 months, measles on two occasions at 4 and 5 years and also illnesses diagnosed as diphtheria and malaria also in the fourth and fifth years.

Physical Appearance on Admission. The patient was an obese youth, 5 feet 6 inches in height. The fat was well distributed over the entire body, being only slightly thicker over the abdomen and hips without hanging in folds. The hips were large in relation to a smaller chest and slightly narrow, rounded shoulders. The arms measured 11¾ inches, the chest at the nipples 38 inches, the waist 36¼ inches, the hips 43 inches, the mid-thigh 26 inches and the calf 14 inches. The patient weighed 189 pounds, which was about 50 pounds overweight.

The skin was clear, thin, soft and sweating. The hair on the scalp was black, straight and medium in thickness. The eyebrows were wide and dark. There was no beard. The pubic hair was dense and of female distribution. Black hair was present on the legs but was absent on the arms and chest.

The head was somewhat large and the face was long. The occipital-frontal circumference was 21¾ inches. There were no irregularities. The ears were large and long with free lobes. The nose was well formed. In the eyes the iris were brown, the conjunctivae were clear and the retinal pigment was excessive, evenly distributed and with no post-inflammatory deposits. The nerve-heads were clearly outlined. The teeth were perfectly formed, white, and there was no dental work.

The thyroid was not enlarged. The supraclavicular fossae were not obliterated by fat pads. The cervical and axillary lymph glands were normal. The thorax was grossly symmetrical. The heart and lungs were normal. The pulse rate was 76 and the blood pressure 110/60.

The abdomen was regular in contour and there were no masses or enlarged organs. Both testes were descended but were small, about ¾ inch in diameter. The penis was small, being about 3 inches long. The rectum was normal.

The bones were adequate and long. The fingers tapered at the end, and the joints were abnormally mobile. Extension at the carpo-phalangeal joint was 260°. The scapulae were mildly scaphoid. The legs rotated incompletely medially so that the feet toed out almost at 90° on standing. There was slight eversion of the feet. There was exaggerated upper dorsal curve and lordosis.

Neurological Findings. The vision was 20/20 and the fields were normal. Color vision was imperfect for anything but simple primary colors. The hearing was equal in both ears (8 seconds through bone, 12 seconds through air for 100 vibrations per second). Articulation of test phrases was poor, probably on account of the mental deficiency. He does not sing or recognize tones. Other cranial nerves were normal. The superficial reflexes were diminished and there was no cremasteric reflex. The tendon reflexes were normally active and equal. There was equalized muscular weakness, especially of the hands. The grip was 24-26 kg.—that of a thirteen-year-old. There were irregular pseudo-athetoid movements of the hands. The boy did not stand perfectly erect except for a few seconds, then scoliosis appeared, or he took the chance to flop into a chair. Skilled movements were poorly performed.

Mental Findings. This patient was an awkward, obese boy, extremely careless about his appearance, allowing himself to become dirty and to generate a very noticeable body odor. He preferred to sleep most of the time and was frequently angered and quite resistive to any efforts to get him up. Hunger alone seemed to be the one drive that would get him out of bed. Emotionally, he was very unstable, crying on the least provocation and becoming happy again because of

a few words of praise. Despondency overtook him the moment he was alone, but when with others he talked in a loud, exhibitionistic manner, continually monopolizing the conversation, frequently staging stories and scenes to gain attention. Once he was hysterical for days, simulating some sort of spasm and screaming loudly during his entire waking period. He argued often, using borrowed phrases and no reasoning. If his schedule called for anything he did not care to do he would go to sleep, refusing to be roused, or would insist that it deprived him of his freedom which the constitution gave him. He acted like an unstable child of ten or eleven years.

Psychometric Findings. The patient coöperated well and his memory was good. Association was fair but he had few ideas. All responses were a little slow. The mental age was 10 10/12 and the I. Q. was 68, revised to 77. The average performance level gave a mental age of 13 years.

Laboratory Findings. The haemoglobin was 90 per cent, the red blood cell count was 5,100,000, the white cell count was 6,000, the neutrophiles were 61 per cent, small leucocytes 36 per cent and large leucocytes 3 per cent. The urine was acid, the specific gravity was 1.028 and albumin and sugar were not present. The blood Wassermann test gave negative findings.

The glucose tolerance test showed a fasting blood sugar of 0.095 per cent; one hour after ingestion of 150 gm. glucose the blood sugar was 0.125 per cent; two hours later it was 0.121 per cent; three hours later it was 0.93 per cent, and after four hours it was 0.095 per cent. Glycosuria did not appear at any time throughout the test.

X-ray Examination. The skull appeared to be somewhat thickened. In the sella turcica the posterior clinoid process was quite prominent, approximating the anterior clinoid process. There was an impacted lower third molar visible. The hands showed normal ossification.

Course in Sanitarium. On admission, the patient was much pleased to have a room alone. For two or three days he lay around in his room, napping, and reading the comic sheets. He was proud to display his capacity to eat twelve pancakes and drink five or six glasses of milk at a meal. His appearance was that of a careless, disheveled youth with unkempt hair, dangling untied shoe strings, and opened shirt collar.

Within the first week he began an active part in the recreation. He tramped with others on the hikes, coming in last, and always exhausted. He went in for tennis, but his clumsiness lost him every game. After losing a match with a player he knew was poor, he became depressed, slept poorly at night and began to have night terrors with occasional loud talking and singing while asleep. Following an active day in his second week, he broke into a prolonged attack of unnatural laughter. This recurred but gradually was supplanted by crying spells, which at first gained him attention from the nurses and doctors. In such attacks he would be inconsolable, and would voice the fear that someone was choking him, and that he couldn't get air. During the third week, he once became combative, crying and yelling, kicking and fighting. When finally quieted, it was "people hate me; nobody here likes me; I can't play tennis."

At the beginning of his fourth week he was up and out again, momentarily interested and making fair progress in simple basket weaving. His tennis improved under the patient tutelage of a male patient. But more difficulties followed when he was placed on a schedule forcing him to rise at 7:30 a.m. instead of 10 or 11 a.m. Temper tantrums reappeared, which when unnoticed, provoked even further retaliative efforts. He improved momentarily again with admission to swimming classes and excursions, the only sport in which he could excel, but on one occasion, eluded his attendant and hid out until midnight. He obtained a kind of satisfaction in creating a scene of any kind, sobbing in a remarkably loud, yowling voice, snatching others' food, throwing water, and even fighting with the nurses—all of which might be provoked by a request to follow his schedule, keep his appointments, or appear on time at meals. He would often exaggerate or falsify in his own behalf. Often in his fury, he would threaten to kill the nurse, or himself, and once made a feeble attempt to hang himself with a handkerchief. On other occasions of stress, he would shout, "you're driving me to the reformatory! I'll commit some crime!"

In his tenth week he was given the job of stage manager of a puppet show, which seemed to produce a marked change in his behavior. He rose early, studied, took a keen interest in his appointments, watched his dress. And with this change he rapidly gained insight into his own possibilities and behavior. He was given

more freedom, and became visibly happy. A few days before his discharge, he came to the doctor, saying he was going to have another of his spells, complaining that he couldn't "hit a nail," "nobody understands but you." His failures again threatened his adjustment, but with reassurance, and an explanation that he would understand any outbreak he might have and not hold it aginst him, he calmed without any serious break. In two days his restlessness, resentment, and tension had disappeared. A few days later he took the train home alone.

Throughout the hospitalization period we saw repeatedly failures resulting from attempting activities beyond his physical and mental capacity. These failures resulted in fury, tantrums, misbehavior, and falsification, with a flight to childish rebellion or dependence.

Therapeutic Results. He received anterior lobe pituitary extract in 1 cc. doses for the first two weeks, which were stopped because of a period of excited behavior. Simultaneous with this he was given desiccated thyroid gland, 2 grains three times a day, which was also stopped after the second week. At the beginning of the fifth week, he was placed on whole lobe pituitary extract, which was started at 1 cc. dose, and gradually increased to 2.5 cc., which caused blanching, and slight headache. Otherwise the patient thought he felt better and requested the "shots" be continued. The thyroid was again renewed at the fifth week, and continued at a dose of 3 grains daily. The basal metabolism at the 8th week was plus 16, and the pulse running about 90. The following week (9th) the pulse increased to 120, and the thyroid was reduced to one grain daily. The pulse slowed and receded to around 75 in the 12th week, at which time the basal metabolism had again fallen to minus 13.

The results of the endocrine treatment were not striking; his psychotherapeutic conferences were probably as largely responsible in the improvement in his behavior as the endocrine treatment. In addition the dietary restrictions were probably in part accountable for his loss in weight. His basal metabolism was raised from minus four to plus 16, probably due to the thyroid medication, only to fall to minus 13 after reducing the thyroid dosage to 1 grain daily. He lost in weight from 189 pounds to 174 pounds.

This patient was seen in frequent psychiatric conference of an hour's duration over a period of more than two months, during which time he gained much insight into the nature of his behavior and the motives for it.

Physical Examination After Three Months. In general appearance he was still obese, but the loss of 13 pounds in weight was shown in his face and his body where the folds of fat were looser. The chest, waist and thigh measurements were 2 to 2½ inches smaller, and the arms were ¾ inch smaller. The physical findings were essentially normal or were the same as previously reported. The hair distribution was still of the female type, the testes were small and there was no cremasteric reflex. However, erections had appeared infrequently for the first time while playing tennis. The blood pressure was 92/35, the pulse rate was 65 to 85 and the final weight taken was 174 pounds.

Neurological Findings After Three Months. The color vision had improved slightly but definitely, but tiring was an evident factor in that he made a gross error at the last in confusing green and brown. The knee jerks were slightly more active. Skilled movements of rapidity were poorly performed as before.

Psychometric Findings After Three Months. The I. Q. had risen from 77 (mental age 10 10/12) to 91 (mental age 12 3/12).

SIBLINGS

The twin brother had also had much difficulty in school work and occasionally resorted to lying but apparently had been much more favored by his mother than had the patient. Because of his more quiet, retiring manners he had gotten into much less difficulty in school and social situations, and consequently had more friends and appeared to make a little more intellectual progress. His physical examination showed primarily the same obesity, genital hypoplasia, and mental retardation, but did not show any retinitis nor any diminution in visual acuity though there was slight deficiency in hearing.

PHYSICAL EXAMINATION OF TWIN BROTHER

The bodily appearance, complexion and configuration were the same as those of the patient. This boy was 12 pounds heavier, although his height was the same as that of his twin. The chest development was better and was three to four inches larger in circumference. The waist line was larger and the hips and thighs were the same. The arms were 1¾ inches larger.

The eyegrounds were pale without excessive pigment.

There were several fillings in the teeth. The uvula was small and could hardly be differentiated from the palatal roof.

The chest sounds were resonant with slightly diminished breath sounds at the right base where there was a three-inch scar (empyema) at the 8th space. The mammae were prominent.

The pulse rate was 72 and the blood pressure 94/54.

The genitals were small although the testes were slightly larger than those of the patient.

The fingers were tapering and were hyperextensile.

Neurological Findings. The color vision was nearly perfect, with only two mistakes made in twelve pale shades. In the hearing tests the bone conduction lateralized to the right. It was practically the same for 100 as for 256 vibrations per second (6 seconds through bone and 12 seconds through air). The tendon reflexes were active and equal. The knee-jerk was slightly hyperactive. Muscle power and coördination in skilled acts were similar to those of the patient. However, this twin could write and draw much better.

Psychometric Findings. The I. Q. was 69, revised to 81 (mental age of 11½ years).

X-ray Examination. The skull was somewhat thickened. The occlusion due to anterior bending of the posterior clinoid process was complete.

PHYSICAL EXAMINATION OF THE YOUNGER BROTHER

This boy was 14 years old, was 5 feet 4 inches in height and weighed 134 pounds—which was 20 per cent overweight. The hips were definitely large, being 2 inches larger in circumference than the chest (33½ compared to 31½ inches). The waist measured 28 inches. There was a melanochromic area 2 x 1 cm. (pigmented hairy mole) on the inner side of the left eyebrow which had been present from birth. The skin was otherwise clear and was warm and moist. The mammae were somewhat prominent. The chest expansion was two inches. The blood pressure was 100/56.

The testes were small (1x¾x½ in.) but the penis was larger than that of the patient or the other twin.

The extremities were normal. The muscle power was good (grip 24-28 kg.). Coördination was normal and he performed skilled acts well. Writing and drawing were only fair.

The eyegrounds were normal.

Neurological Findings. Color vision and night vision were normal. The hearing for 100 vibrations was 8 seconds through bone and 12 seconds through air and was lateralized to the left.

Psychometric Findings. The I. Q. was 80, revised to 86 (mental age of 11 8/12 years).

SUMMARY

The case here described in detail seems to fit into the category of the Laurence-Biedl Syndrome and the patient's identical twin also shows misbehavior, mental retardation and similar physical abnormalities. The mental retardation is probably due to the cerebral deficiency; the behavior problems are largely the result of the patient's attempts to fit into family, intellectual and social siuations beyond his physical and mental capacities. The result is an emotional disturbance, delinquency and antisocial behavior. We feel that such patients should have the benefit of endocrine treatment

but that psychological reorientation and readjustment at a simpler level is probably even more important.

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ROENTGEN THERAPY OF EXOPHTHALMIC GOITER

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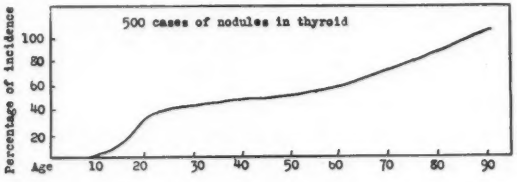
In beginning a discussion of toxic thyroid conditions it is advisable to make clear just what is meant. In many places the toxic adenomas and exophthalmic goiters are considered to be different stages of the same disease. In the clinic they were considered as two distinct entities, and were treated as such. The statistics of the prevalence of adenomas of the thyroid as compiled by Dr. Carl Rice of the Department of Surgery of the University of Minnesota show definitely that nontoxic adenomas are present in about 80 per cent of the population of Minnesota; this prevalence increases with age (chart). These adenomas have a tendency to become toxic in later



life. In the exophthalmic group the opposite was found; it is rare in childhood; is most frequent in the second or third decade, and is again rather uncommon in older people. The chief difference is in the clinical findings of the two diseases. Up to a certain point toxic goiters are the same; from then on exophthalmic goiter has one or more of the following characteristics: (1) a very definite eye change in a large percentage of cases; (2) a bruit over the superior poles of the thyroid; and (3) a peculiar nervousness. All the symptoms of toxic adenomas of the thyroid, hyperthyroidism, can be duplicated by the administration of thyroxin or thyroid extract. Those symptoms found only in exophthalmic goiter cannot be reproduced in either man or animals. The toxic adenoma makes the body sick, and adversely, in exophthalmic goiter the body apparently makes the thyroid sick.

On this basis there is no question but that surgery is the logical treatment for adenomas. In true hyperthyroidism, the excessive thyroid should be removed, but in exophthalmic goiters a different condition is dealt with, and up to the present time surgery has been the only real means of relieving its symptoms. That surgery does not always relieve the cause is shown by the fact that in cases in which there has been an almost complete removal of the thyroid gland there has been in a number of cases a complete recurrence of all the symptoms within a period of from four to six weeks, up to a few years, with only a small amount of hypertrophy in the remaining gland.

The recurrent cases, even with only a very small amount of thyroid tissue present, have basal rates as high as they had with the original or primary change in the thyroid. In the past two weeks two cases have been seen with total ablation of the thyroid for exophthalmic goiter with auricular fibrillation. One patient who had a basal rate of plus 61, after six weeks has now a basal rate of plus 4. The other patient with a basal rate of plus 40, preoperatively, has now, after three months, a basal rate of minus 4. In both patients the pulse is slow and regular at the present time, but neither one shows any signs of myxedema. In the surgery of toxic adenomas of the thyroid in which large amounts of tissue are removed, e.g., tissue outside of the nodule, the result is always a low basal rate, and a tendency toward myxedema.

In 1930 at the goiter clinic at the University of Minnesota the records show that 17 per cent of all the patients admitted to that clinic had recurrent exophthalmic goiter. This made an average of 22 per cent recurrent toxic goiters and 78 per cent primary toxic goiters. The majority of this group were extremely toxic and only fair to poor surgical risks. Some of these were put on roentgen therapy. A few of the group of twenty-nine persons treated had primary lesions. This group were all treated by Dr. Albert H. Stenstrom, of the x-ray department of the University of Minnesota, with the deep therapy machine. These patients all received at first Lugol's solution, but at the present time diiodotyrosine in 0.02 milligram doses three times a day is being used in a group of cases, with a supernourishing diet and plenty of rest, but unless there is an extreme amount of cardiac damage the patients are not confined to bed. The roentgen therapy consists of: A first series of treatments given to an anterior field which includes the cervical region and the upper portion of the sternum. It is given in four portions over eight to fourteen days. A total of 140 per cent of a skin erythema dose (or about 1000 roentgens) is given. A second series is usually considered necessary and is given six weeks later. Lateral fields are used. Each lobe receives about 120 per cent of a skin erythema dose in two treatments, the total dose being applied in eight days. Two hundred kilo volts, one-half or one millimeter copper, plus four millimeter aluminum filter and sixty centimeter target skin distance are used.

As a great many of the patients came in from the country it was hard to take frequent basal readings. The charts will show some of the reactions following the treatment. These seemed to follow two definite courses: (1) Those in which there was a positive increase in the basal rate following the first x-ray treatment, and (2) that group in which there was a determinate drop in both the basal rate and the percentage of disability almost immediately after the first treatments. The following is an example of the first group.

H. S. (Figure 1) came to the clinic complaining of typical exophthalmic symptoms, with a severe heart complication. She had been refused surgery at the University Hospital. On Lugol's solution her basal rate dropped from plus 67 to

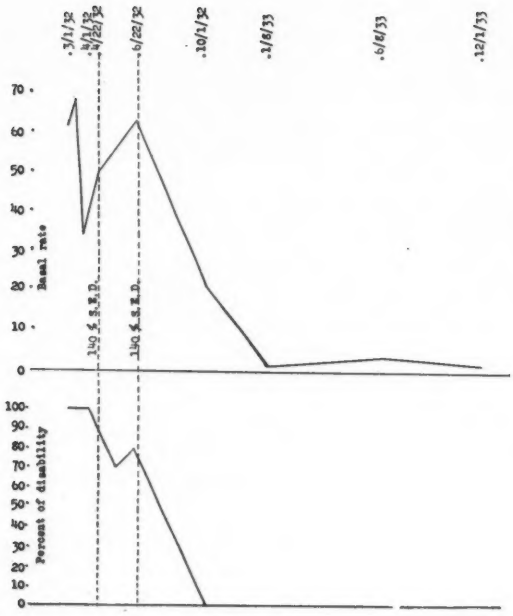


Figure 1

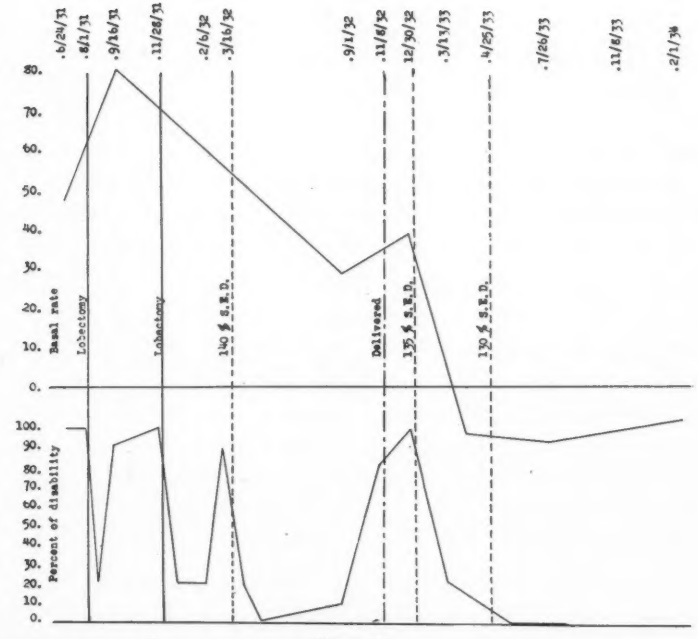


Figure 2

plus 33. The basal rate started up again, and when it was plus 50 she received a series of x-ray treatments of 140 per cent of a skin erythema dose. The basal rate continued to rise to 62 and after the second exposure of 140 per cent of a skin erythema dose the basal rate dropped immediately to zero, and simultaneously the per cent of disability dropped almost to zero.

The above type of reaction took place in eight of our cases, or 38 per cent.

An example of the second group, e.g., the group with immediate response to treatment, is shown as follows:

A. P. (Figure 2). After two lobectomies there was a very definite increase of all symptoms. After 140 per cent of a skin erythema dose there was a very definite drop, not only in the basal rate, but especially in the percentage of disability. It is interesting to notice what the last few weeks of pregnancy did to the basal rate as well as the amount of work this person could do. This encouraging response to x-ray treatment took place in eleven cases, or 52 per cent.

In two, or 10 per cent, of our patients there was at no time an appreciable change either in basal rates or symptoms.

Questionnaires were sent to the twenty-nine patients treated with x-ray for exophthalmic goiter. From the twenty-one replies received, sixteen, or 76 per cent, showed satisfactory results, five, or 24 per cent, showed unsatisfactory results. A brief summary of the five unsatisfactory cases follows:

(1) This patient had a marked drop of basal rate, and improvement in symptoms after treatment. Her friends thoroughly convinced her that only surgery would help, so she had a thyroidectomy elsewhere.

(2) The basal rate was always in normal range. He had had a diagnosis of toxic goiter outside the clinic, and had taken Lugol's solution. He showed some positive signs of hyperthyroidism. The x-ray treatment apparently had no effect on either the symptoms or the basal rate.

(3) This patient had recurrent thyroid symptoms. She always had a different complaint. She had one x-ray treatment and refused further treatments. After a subtotal thyroidectomy she says that she is now well.

(4) This individual had definite improvement after the first treatment. As she was a blonde her skin became exceedingly tender, and she requested surgery rather than a second course of treatment, although she showed marked improvement both as to basal rate and clinical symptoms after the first treatment.

(5) This patient had decisive clinical and laboratory improvement. A thyroidectomy was performed to relieve pressure from a substernal mass. The microscopic slides of the adenomas removed showed a degeneration of the encapsulated tissue.

We recently sent out follow-up questionnaires to a group of patients, first to those who had had operations for exophthalmic goiter, and secondly to those who had been treated with deep roentgen therapy. We tried to

grade the improvement numerically so that we would have some way to compare the results of the two series. The following chart shows our results:

	Surgery	X-Ray
Perfect (100% improved)	24%	19%
Excellent (85% to 98%)	48%	43%
Good (75% to 84%)	9%	14%
Fair (50% to 74%)	5%	0
Poor (1% to 49%)	3%	9.5%
No improvement	9.6%	14%
Died subsequently	2.4%	0

This tabulation shows good results in 81 per cent of those surgically treated, 76 per cent in those treated with the deep x-ray therapy.

During the past five years I have had opportunity to study a large number of exophthalmic goiter patients. These have been treated in various ways. All have been put on iodine in some form, usually with the typical response to treatment. Some have been kept on small doses of one to two minims of Lugol's solution a day over a long period of time, and have remained symptom-free. Others have had thyroidectomies, and a third group have had the previously described treatment with roentgen therapy. At first, the roentgen therapy was used as a palliative measure to be followed by surgery in severe cases, e.g., those in which it was thought that the surgical risk would be too great due to the poor response obtained in the use of iodine, the extreme toxicity of the goiter, or to other complications. It also was used on patients whose finances did not permit a protracted period of hospitalization. In none of our cases did we get either a precipitate crisis following treatment, nor any perceptible nervous reaction. The response to treatment by these patients was so satisfactory that subtotal thyroidectomies have not been deemed necessary nor advisable. A comparison of the end results of surgical and x-ray treatments show that they are about the same. The basal rate no doubt drops faster after surgery than after x-ray treatment, but the two reach normal as to complete rehabilitation at about the same time.

SUMMARY

In a group of twenty-nine patients with exophthalmic goiter, mostly recurrent cases, treated with roentgen rays we were able to follow up twenty-one cases. This group showed a definite improvement clinically, in all but five cases, after the first course of treatments. Some patients needed two courses of treatment, and a few a third course. In this group we had 76 per cent satisfactory results, while the surgical clinic reports 81 per cent satisfactory results. We have no deaths to report; the surgical clinic reports 2 per cent.

PITUITARY HEADACHE

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Eleven cases of pituitary dysfunction have come under observation during the past four years with the characteristic symptom of headache. Of the eleven cases studied, three are given in detail. These are characteristic of the series as far as apparent etiological factors, symptomatology and treatment are concerned. One of these cases is outstanding, in that this symptom complex was found in the male and relieved by treatment.

The ovarian pituitary headache can be explained by the work of Doisy, Allen and Novak. During the end of the intermenstrual period the gonad secretions wane and the pituitary thus escapes from their checking influence. The pituitary increases in size and causes the intracranial pressure to be increased. If the sella is smaller than normal, the pain is increased with hypertrophy of this gland. As the process continues there may be even destruction of the bony cavity in which the gland is contained. This process may continue until all semblance of the original sella has disappeared and with this the headache also disappears. This hypertrophy of the gland may continue until it causes pressure on surrounding structures with symptoms of optic nerve disease (choked disc, partial or complete blindness); involvement of the third, fourth, fifth and sixth nerves, with impending symptoms of hypo-pituitarism.

There is much speculation and controversy as to the cause of intracranial pain. The brain substance in itself is not sensitive, but Leak, Lovenhart, and Muehlberger feel that the pain sense lies along the cerebral blood vessels. They mention the fact that after the dura is cut there is no pain in the parenchyma of the brain. They found there was no sensation either in the dura or brain if the blood vessels were not cut or traumatized. According to Cushing the pain is produced by increased intracapsular pressure of the pituitary. Incision of the capsule has stopped the headaches. Is it not possible therefore to increase the intracranial tension by hypertrophy of the pituitary enough to cause pressure on the nerves surrounding the vessels and sufficient pressure to increase the intracapsular tension of the pituitary gland to produce the so-called headache? A hypofunction causes the increased tension by increasing the size of the gland. This produces pressure on the nerves surrounding the blood vessels, and increases the intracapsular pressure, resulting in pain. This hypertrophy is relieved by supplying the needed hormones to the body. With this additional aid the pituitary gland will resume its normal size and the headaches will cease.

Many clinicians report good results with either anterior or posterior gland therapy, by either oral administration or subcuticular injection.

The subjects treated have responded best to posterior gland therapy. Both oral and subcutaneous methods have been employed.

Case 1. Mrs. C. A., a white Italian woman, aged 45, was examined on December 22, 1930. Her headaches had been intermittent for the past five years, but for the last two or three months had been gradually getting worse. They were splitting and expansive in nature, usually waking her out of a sound sleep at one or two o'clock in the morning. They lasted from one to ten hours. At first the headaches occurred just before or during her menstrual periods, but at the time of the examination they were coming every morning. The pain began in the occipital region and radiated to both temporal regions, with severe pressure in the eyes. The eyeballs were very sensitive to pressure. At times there had been nausea and vomiting, some dizziness and hot flashes. She became very weak and quite dyspnoeic. She got very little sleep on account of the severity of the headaches, and medication had not relieved them.

Her menstrual history began when she was twelve years of age and was of the regular 28-day type. There was no pain until five years before when the severe headaches began. These were more severe with the menses. She had nine living children and the youngest was five years of age. She had had two miscarriages, the last one two years before.

The physical examination showed a short, fat, restless, Italian female. Her gait and posture were good. Her height was 63 inches and her weight was 251 pounds. There was no excessive hair growth. She had definite girdle fat with large pendulous breasts. Her hands and feet were small. The skin was soft and moist and the secondary sex characteristics were female. The scalp was sensitive on pressure mostly over the occipital and temporal regions. The eyes were large with slight exophthalmos. The fundi were normal. The thyroid was small, but firm and sensitive. The heart and lungs were normal. The heart rate was 64 and the blood pressure was 122/92. The abdomen was very fat with a large umbilical hernia and with a fat apron hanging over the mons. The uterus was large, boggy, and retroflexed. The tubes and ovaries could not be palpated because of the fat abdominal wall. The reflexes were generally sluggish.

The blood examination showed the following: haemoglobin, 65 per cent; red cells, 3,520,000; white cells, 4,200; polymorphonuclears, 60 per cent; small lymphocytes, 28 per cent; large lymphocytes, 10 per cent; and eosinophils, 2 per cent.

The basal metabolic rate was plus 12 per cent.

In the urine examination albumen was found to be one per cent and there were a few hyaline casts.

The blood chemistry was normal.

The Wassermann test gave a negative reaction.

An x-ray examination of the sella turcica was not made.

Treatment consisted of ½ cc. Infundin every other day until six doses had been given. There was complete cessation of the headaches. She reported one week after treatment and had a slight headache which was completely relieved with ½ cc. of Infundin. A week later she again reported with a severe headache, and was given 1 cc. of anterior lobe extract but without result. She was completely relieved with ½ cc. of Infundin.

When last heard from this patient still reported relief from her headaches. At no time did she take any oral medication and her blood pressure did not increase beyond 130/96.

Case 2. P. C. was a white, unmarried man, aged 40. He was examined December 31, 1930. His headaches had started without apparent cause twenty years before. At first they occurred only at certain times each month, and lasted two or three days. For five years previous to the examination the headaches were continuous. Sleep had no effect on the pain, which was expansive in nature, starting in the occipital region and radiating to the temporal regions. The occipital and temporal regions were tender on pressure. Pressure on the scalp seemed to increase the pain. There were shooting pains over both jaws, but were more severe on the right. Fatigue had no effect on the pain. Certain foods such as rare beef in any form increased the headache. His sex life was normal. Excitement and sexual excesses increased the headache. The pain could be relieved but not stopped with coal tar derivatives such as aspirin or acetanilid. Alcohol had no effect on the pain. There was dizziness on stooping with pounding in the eyes and head. At times there was some nausea and vomiting. There was general weakness, irritability, restlessness, and melancholy to the point of self-destruction. His work as a dentist could not be carried on because of continuous pain. His

eyes were fitted with glasses, but this gave no relief. His teeth had been extracted, but this gave no relief. His disposition was very disagreeable, and all interest in life or work was lost. Moving the eyes to either side caused pain in the sockets to such an extent that he turned his head instead of his eyes. He slept poorly, awakening with the usual headache.

Physical examination showed a well-developed, white, American male. He was restless and nervous. His height was 68 inches and he weighed 160 pounds. The general characteristics as well as the secondary sex characteristics of this individual were masculine. His torso was short and he had rather long arms and legs. The gait and posture were normal. There was some tenderness over the occipital and temporal regions. The hair was thin and the eyes were large with a slight exophthalmos. The eyeballs were sensitive on pressure. The fundi were normal. The teeth were very irregular and were small and close together, with an overriding lower jaw. The thyroid was soft and normal in size. The lungs were normal. The heart sounds were normal, the pulse rate was 86 and the blood pressure 122/98. The abdomen, penis and testicles were normal, as were the reflexes. X-ray examination of the sella turcica showed it to be slightly smaller than normal size. There was well-marked polypoid thickening of the mucous membrane of the sphenoid sinus and calcification of the pineal was also well marked.

Blood examination showed the following: haemoglobin, 90 per cent; red cells, 4,760,000; white cells, 9,600; polymorphonuclears, 70 per cent; small lymphocytes, 24 per cent; large lymphocytes, 4 per cent; and transitional forms, 2 per cent.

The urine examination gave normal findings.

The basal metabolic rate was plus 5 per cent.

The blood chemistry was normal.

The Wassermann test gave negative findings.

Beginning on December 31, 1930, Infundin (B.W.CO.) in ½ cc. amounts was given for eight days. This medication relieved the headache entirely. On January 8, 1931, there was a slight headache, but different in type. The blood pressure was 116/78. The Infundin was discontinued and the patient had no headache for four weeks. This was from January 12 to February 18, 1931. Infundin was then given three times a week, with a slight headache at times. On March 2, 1931, anterior lobe was given hypodermically. There was no headache at the time this was given. There was severe headache on March 3, 1931, at 6 a.m. It was relieved the same day with Infundin. During this period the blood pressure which had fallen to 112/60 gradually rose to 140/98. On April 6, 1931, the patient reported with a severe headache. He had had no treatment for fourteen days. He was given ½ cc. sterile water subcutaneously with no relief of pain. At this point whole pituitary (B.W.CO.) was started orally, but there was no relief except when Infundin was used. Anterior lobe was then started orally with the same result. On May 1, 1931, posterior lobe tablets (grains ½) were given in addition to the subcutaneous injection of ½ cc. Infundin. The headaches were relieved until September 15, 1931, when ½ cc. Infundin relieved the pain within fifteen minutes. From then until May 10, 1933, the patient reported for subcutaneous injection every two to six weeks. He took ½ grain of posterior lobe daily. From May 10, 1933, to August 25, 1933, it was not necessary to have a subcutaneous injection of Infundin as long as he continued his posterior lobe tablets. This patient described the relief as life giving, as if life were worth while and that five minutes following the subcutaneous injection of Infundin there was a sensation as if a heavy load were lifted with a shrinking sensation in his head. The pressure in the eyes was relieved at the same time. The sensitiveness of the scalp and eyes remained for several hours, and then disappeared.

Case 3. Mrs. E. L., a white, married female, aged 36, was examined October 16, 1931. Her headaches had started when she was fourteen years of age at the onset of menstruation. These headaches were of the expansive type, coming on at first two or three days before and lasting through the period. Then as the years progressed the headache did not seem to bear any relation to the menstrual flow but came with overexertion, worry, excitement and the like. The pain would begin in the occipital region and radiate to both temporal regions. There was considerable dizziness, roaring in the head, buzzing in the ears, nausea and vomiting. Stooping caused a pounding in the head and eyes. The eyeballs were usually sensitive to pressure, before the headaches. There was pressure and feeling of fullness in the head. Usually preceding the headache there would be a fit of uncontrollable temper. During the last six months the headaches had been present nearly every day, but were being controlled with coal tar derivatives. The menstrual periods which began at the age of fourteen were regular and there

was considerable pain which lasted the entire period. Fifteen years before she had had a currettment which relieved most of the pain. The menses had been scant at times. The physical examination showed a short, plump, white, American female. She was nervous and her gait was somewhat "staggery." She was 60 inches tall and weighed 140 pounds. There was no excessive hair growth. The secondary sex characteristics were female. The scalp was sensitive over the occipital and temporal regions with referred pain downward over the mandible. By x-ray examination the sella was found to be rather small. The fundi were normal. The teeth were poor and several abscesses at the apices were shown by x-ray examination. The throat was congested. The thyroid was normal in size, consistency and position. The lungs were normal. The heart sounds were loud and pounding, and the rate was 96. The blood pressure was 168/92. There was some tenderness in the upper right quadrant of the abdomen and also in the lower right and left quadrants. The uterus was small and sensitive. The ovaries and tubes could not be palpated. X-ray examination revealed a diseased gall-bladder. The reflexes were hyper-active. The spinal fluid was normal. Spinal and blood Wassermann tests gave negative findings.

The blood examination gave the following: haemoglobin, 80 per cent; red cells, 4,320,000; white cells, 7,250; polymorphonuclears, 70 per cent; large lymphocytes, 3 per cent; small lymphocytes, 25 per cent; and eosinophils, 2 per cent.

The blood chemistry was normal with rather a low sugar content (68.9 grams).

The urine examination gave normal findings except for a slight trace of albumen.

The basal metabolic rate was plus 8 per cent.

Infundin (B.W.CO.) in ½ cc. amounts was given daily until four doses had been given. There was complete cessation of the pain. Then Infundin was given every other day for four doses. Two ½ grain tablets of pituitary posterior lobe were given daily, with Infundin once a week for four weeks. The blood pressure on December 15, 1931, was 140/86 and remained there indefinitely. The abscessed teeth were removed on August 15, 1932. This improved her condition so that no Infundin was needed and one or two tablets of posterior lobe sufficed to control the pain. When last seen she was having rather severe headaches, but refused further treatment. To our knowledge the gall bladder had not been removed or treated. Anterior lobe extract gave no relief whatsoever. She is not under treatment at the present time and is suffering with repeated attacks of headaches.

A summary of the cases herein reviewed is merely a confirmation of previous reports with the exception of the male. It is rather peculiar that one clinician will get results with whole gland, another with anterior lobe, and still others with the posterior lobe. The first case falls in the class of hypo-pituitarism of menopausal origin. As no x-ray examination was made of the sella it is impossible to state whether there is an erosion or enlargement. The second case, that of the male, is a definite posterior lobe deficiency disease, due to chronic infection of the sphenoid sinus, with a calcified pineal gland which is not unusual as pineal sand is found in adult life. There does not seem to be any connection between this calcified gland and the headache that can be demonstrated in a physical manner. The third case is a hypofunction again of the posterior lobe due to multiple foci of infection of teeth, gall bladder and pelvis. None of these cases have been benefited by the anterior lobe treatment. As a consequence, I am at a loss to explain the cause of the headaches of these three distinctly different types of patients, other than as mentioned above, each with a different and distinct etiological factor, but all three controlled by the same medication—the posterior lobe hormones. The cause, therefore, of the headache is explained by an interglandular syndrome which forces the pituitary gland to hyper-activity, thus causing it to hypertrophy. As it is contained in the

"small skull within the large skull" there is an increase of intracapsular pressure which produced pressure on the blood vessels and their nerves and the pituitary capsule, and thus pain.

The sudden and lasting relief received by these patients is remarkable. It is evidently due to the shrinking of the oversized gland and relieving the pituitary of hypofunction. There is indication that there is a pronounced hypofunction in many cases where characteristic pain in the head called headache would indicate hypofunction.

SUMMARY

Eleven patients suffering from pituitary headache (ten females and one male) were treated with posterior pituitary extract by mouth and subcutaneously—with disappearance of the headaches. The oral treatment consisted of the posterior lobe extract in tablet form and the injections were the posterior lobe extract, Infundin. The case histories of three of the patients are given in detail. Extracts of the anterior lobe apparently were without benefit.

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THE REPAIR OF THE REPRODUCTIVE SYSTEM OF HYPOPHYSECTOMIZED FEMALE RATS BY COMBINATIONS OF AN HYPOPHYSEAL EXTRACT (SYNERGIST) WITH PREGNANCY-PROLAN*

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It is now well known that the substance present in the urine of pregnant women (prolan) provokes characteristic changes in the ovaries of immature mice or rats—changes which consist essentially in the growth of the ovarian follicles, in ovulation, and above all, in luteinization whether of ripe or unripe follicles. It has been equally well established that these changes are more difficult to secure by the administration of this substance to hypophysectomized females (1) (2).† These circumstances led naturally to the assumption that the pituitary gland itself contributes in some obscure way to confer gonadotropic effects on prolan. We sought further support for this hypothesis by adding various hypophyseal extracts to prolan to ascertain whether they would enable prolan to exert the above-mentioned effects on the ovaries of hypophysectomized females (6). The gonads of hypophysectomized female puppies had been found to be unresponsive to prolan, though treated for a period of 2 months with high daily dosage. Laparotomy performed after this period of injection showed the genital system to be in an infantile or atrophic condition, an interpretation supported by microscopic study of an excised ovary. On the other hand, the treatment of such puppies with combinations of prolan with hypophyseal extracts caused prompt and outspoken changes in the structure and function of the reproductive apparatus. The hypophyseal extract used contained considerable amounts of growth hormone, but only negligible amounts of gonadotropic substance, so that its coöperation with prolan was all the more striking.

It was also immediately possible to show that pituitary extracts, when combined with prolan, intensify the normal effects of prolan on the ovaries of normal immature animals (7) (8) (9). Employing this method of study, a considerable effort was then made to determine so far as was possible the nature of the pituitary substance thus intensifying prolan effects (10) (11). The provisional designation, *activator,* or *synergist,* has been used for this substance. The synergist has been prepared free of the

*Aided by grants from the Rockefeller Foundation of New York, and the Board of Research of the University of California.

†Other changes consisting essentially of thecal hypertrophy have been recognized by Noguchi (3), Collip (4), Smith (5), and others. We can confirm their findings.

growth, thyrotropic and lactogenic hormones and possessing only traces of gonadotropic hormone.*

While the use of normal immature animals thus facilitated the study of the nature of the synergist and of methods of purifying it, it is only by the employment of hypophysectomized animals that a test can be given as to whether the synergist imitates the normal hypophysis, for it should enable prolan to give gonadotropic effects in hypophysectomized animals fully equal to those which it exerts on normal animals. This paper is hence devoted to a report of the effect of the synergist alone, of prolan alone and of the combination of the two substances in hypophysectomized female rats.

The preparations of pregnancy-prolan† and the hypophyseal component (Synergist)‡ used in all experiments were carefully standardized in their gonadotropic properties and synergic action in normal immature rats, either previously or co-incident with their administration to hypophysectomized animals. The routine method which has proved satisfactory for the study of activation or synergism is carried out as follows: The hypophyseal fraction (synergist) is dissolved in water and is injected into a group of 3 or more rats, 3 daily injections of 1 cc. per rat being given on 3 consecutive days. The prolan is similarly dissolved and injected into a second group. The same doses of the hypophyseal component and prolan are then dissolved together in the volume of fluid employed above and injected into a third group of rats. All injections are routinely given subcutaneously. Autopsy is performed 96 hours after onset of injection; the ovaries are examined with the aid of a binocular microscope, dissected, weighed, and, when indicated, preserved in appropriate fixative for subsequent histologic study.

Only the results based on animals which proved to be completely hypophysectomized are here reported; incomplete cases were encountered, but were discarded. Complete cessation of growth, atrophy of the lips of the vaginal orifice, failure of the vaginal membrane to rupture and absence of the estrous cycle were valuable indices of the completeness of the operation while the animals were still living. At autopsy, decreased weights of the adrenals, thyroids and gonads offered additional evidence of the completeness of the operation. The final criterion of the success of the operation was based on a thorough search of the sella turcica for residual hypophyseal tissue. If there was any reason for doubting the completeness of the operation, such as the presence of fragments of residual tissue in the region of the hypophysis, the case was discarded.

In the first attempts to determine the effects of prolan, synergist and of their combinations in hypophysectomized rats, adults were used. The

*Unpublished work. In the case of synergist W2228, cited in Table II, treatment of immature pigeons with doses 10 times that employed with the hypophysectomized rats failed to appreciably increase the weights of the testes and did not stimulate the thyroid or crop gland.

†The pregnancy-prolan used in these experiments was a simple alcohol precipitate from urine of pregnant women, kindly furnished us by E. R. Squibb & Son through the courtesy of Dr. J. A. Morrell.

‡The hypophyseal component was prepared from pig or sheep desiccated hypophysis by methods indicated in appropriate places in the paper. The crude hypophyseal material was in part obtained through the courtesy of Eli Lilly & Co., whom we desire to thank.

hypophyses had been removed some time previous to the experiment (70 to 100 days) in order to allow for regression of the reproductive organs, but notwithstanding this long post-operative period, it was found that persisting corpora lutea confused the results. It therefore became evident that the animals should be hypophysectomized before sexual maturity and the appearance of corpora lutea.

For this reason 33- to 35-day-old rats were chosen. The results are summarized in Table I. It can be seen in the table that at the dose level used, the pregnancy-prolan did not stimulate growth of the ovaries. The average weight of 2 ovaries of animals treated with pregnancy-prolan for 10 days was practically the same as that of the hypophysectomized uninjected control (10 mg. as compared with 9 mg.).*

The hypophyseal extract employed for its synergic properties was used at a dose level which gave an average weight for the 2 ovaries of approximately 35 mg. in both the 3-day and 10-day injected groups of hypophysectomized animals, thus causing two to threefold increase in ovarian weight. The histological examination showed a few corpora lutea with enclosed eggs.

When the hypophyseal extract was combined with prolan in vitro, average ovarian weights of 100 and 104 mg. resulted, and histological examination showed that not only more and somewhat larger corpora lutea had been formed but that in some instances ovulation had been produced, as disclosed by finding eggs in the tube.

It was, however, feared that this experiment might not actually indicate the ability of the hypophysectomized animals' ovaries to respond to the combination of prolan and the synergist. The animals were so near sexual maturity when hypophysectomized that the ovaries might have already been affected by pre-pubertal activity of the animal's own hypophysis. Much younger animals, 23 days old, were therefore selected for the experiment, concerning which the preceding criticism could not be made.

As can be seen from Table II, the effects of injecting the 3 substances, the hypophyseal synergist, pregnancy-prolan, or the combination was essentially the same as in the preceding series, and showed that the above mentioned fears were not justified.

Inasmuch as in our experience it is somewhat more difficult to cause increased ovarian weights in hypophysectomized animals when compared with normal ones with such hormones as prolan and the substance in the blood of mares in early pregnancy, it was somewhat of a surprise to observe that the hypophyseal synergist affected the ovaries of the hypophysectomized rats to a degree fully comparable with its effect on the ovaries of young unoperated controls.

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*The larger ovarian weight in the group treated with prolan 3 days (20 mg.) is due to the shorter period of regression between operation and autopsy than in the 10-day injected group. It will be noted that the ovaries of control hypophysectomized animals for the 3-day injected group still weighed 14 mg.

TABLE I

GONADOTROPIC EFFECTS ON NORMAL AND HYPOPHYSECTOMIZED FEMALE RATS OF ADMINISTRATION OF PREGNANCY-PROLAN, HYPOPHYSEAL SYNERGIST AND COMBINATIONS THEREOF.

Type of Animal	Number of Animals	Treatment		Age			Average Weight of Ovaries	Synergism
		Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy		
			Days	Days	Days	Days	mg.	%
Normal	3	Hypophyseal Synergist[1]	3	—	26	30	31	
"	3	Pregnancy-Prolan[2]	3	—	26	30	42	
"	3	Combination	3	—	26	30	151	**175**
"	3	Untreated	—	—	—	30	18	
"	3	Untreated	—	—	—	33	22	
"	3	Untreated	—	—	—	42	25	
"	3	Untreated	—	—	—	48	33	
Hypophysectomized	2	Hypophyseal Synergist[1]	3	33	36–38	40–42	34	
"	2	Pregnancy-Prolan[2]	3	34–35	37–38	41–42	20	
"	2	Combination	3	33	38	42	100	**150**
"	3	Untreated	—	33–34	—	41–42	14	
"	2	Hypophyseal Synergist[1]	10	32–33	37–38	47–48	35	
"	1	Pregnancy-Prolan[2]	10	33	38	48	9	
"	3	Combination	10	33	38	48	104	**207**[3]
"	1	Untreated	—	33	—	48	10	

1. The synergist (W1542) was a 40% alcohol extract of pig pituitary, given in 1.35 mg. total dose per rat, in 3 days or 4.54 mg. in 10 days.

2. The pregnancy-prolan used was an alcohol precipitate from urine of pregnant women, given in total dose per rat in 3 days of 2.73 mg. and in 10 days of 9.1 mg.

3. It may seem somewhat surprising to find the calculated percentage activation somewhat higher in the 10-day injected group (207% as compared with 150%), while the weights of ovaries are about the same. This is explained by the fact that the ovarian weights of the pregnancy-prolan treated animals are smaller in the 10-day series, for the ovaries of these animals have continued to regress notwithstanding the continued treatment. The formula by which activation is calculated is given in the paper cited in reference (10). Only the amount by which the ovary weights resulting from injection of the combination exceed the weights expected on the basis of summation of the gonadotropic effects of the constituents is considered in calculating activation.

TABLE II

GONADOTROPIC EFFECTS ON NORMAL AND HYPOPHYSECTOMIZED FEMALE RATS OF ADMINISTRATION OF PREGNANCY-PROLAN, HYPOPHYSEAL SYNERGIST AND COMBINATIONS THEREOF.

Type of Animal	Number of Animals	Treatment		Age			Average Weight of Ovaries	Synergism
		Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy		
Normal	3	Hypophyseal Synergist[1]	Days 3	Days —	Days 23	Days 27	mg. 32	%
"	3	Pregnancy-Prolan[2]	3	—	23	27	32	
"	3	Combination	3	—	23	27	74	48
"	3	Untreated	—	—	—	23	13	
"	3	Untreated	—	—	—	27	14	
Hypophysectomized	8	Hypophyseal Synergist[1]	3	23	23	27	30	
"	8	Pregnancy-Prolan[2]	3	23	23	27	12	
"	8	Combination	3	23	23	27	60	87
"	3	Untreated	—	23	—	27	10	
Normal	3	Hypophyseal Synergist[3]	3	—	26	30	29	
"	3	Pregnancy-Prolan[2]	3	—	26	30	38	
"	3	Combination	3	—	26	30	151	209
"	3	Untreated	—	—	—	26	14	
"	3	Untreated	—	—	—	30	18	
Hypophysectomized	3	Hypophyseal Synergist[3]	3	23	27	31	32	
"	4	Pregnancy-Prolan[2]	3	23	27	31	13	
"	4	Combination	3	23	27	31	93	151
"	3	Untreated	—	23	—	31	8	

1. The synergist (W1735) was a 40% alcoholic extract of desiccated sheep hypophyses, given in a total dose of 2.73 mg. per rat, in 3 days.

2. The pregnancy-prolan used was an alcohol precipitate from urine of pregnant women; the daily dose per rat was 2.3 mg. or 6.8 mg. in 3 days.

3. The hypophyseal synergist (W2222) used was a trypsin digest of desiccated sheep anterior pituitary. It was given in a total dose per rat in 3 days of 2.7 mg. This product was almost freed of gonad-stimulant (as judged by immature rats), only medium and a few large follicles being stimulated. The preparation was also tested for gonadotropic and thyrotropic activity in immature pigeons. A dose of 27.3 mg. per bird given in 4 daily doses caused no development of testes (40, 33 and 29 mg.) or ovary (52 mg.). (Control testes averaged 22 mg., limits 16 to 38 mg., control ovary averaged 40 mg., limits 29 to 55 mg.). The product showed no thyrotropic or lactogenic activity at this level.

SUMMARY

It is well known that pregnancy-prolan does not exert the same gonadotropic effect in hypophysectomized rats that it does in normal immature rats. It has been shown that pregnancy-prolan combined with certain anterior hypophyseal fractions (synergist) becomes a far more potent gonadotropic stimulant in normal immature female rats. It was hence of interest to test the effect of such combinations on hypophysectomized females. The results from 108 experimental animals, 57 of them hypophysectomized, are here reported.

It has been found that prolan combined with the hypophyseal synergist is just as effective in stimulating the growth of the ovaries of hypophysectomized rats as is the case with normal immature rats, although the ovaries of these hypophysectomized animals remained atrophic after the administration of prolan alone. The synergist therefore, resembles a substance supplied in vivo by the hypophysis of normal rats in intensifying the effect of prolan on their sexual system.

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MAINTENANCE AND REPAIR OF THE REPRODUCTIVE SYSTEM OF HYPOPHYSECTOMIZED MALE RATS BY HYPOPHYSEAL SYNERGIST, PREGNANCY-PROLAN AND COMBINATIONS THEREOF*

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Studies on the action of the hypophyseal substance which in small quantities acts synergically to intensify the effect of prolan in normal immature animals or hypophysectomized animals have hitherto been conducted almost exclusively with females. It has been possible, however, to show that with some changes in the conditions of the experiment, typical synergic intensification of prolan effects can be secured with normal immature males. Nevertheless, as was the case with females, crucial evidence of the action of the synergist must be sought in hypophysectomized males.

A further interest attaches to the gonadotropic effects of this hypophyseal substance on hypophysectomized males for it has been possible to show that in addition to its complementary or synergic action when combined with prolan, when it is administered alone it exerts selective effects on the testes of hypophysectomized males. The hypophyseal material in question administered at the dose levels and for the time intervals herein reported, unfolded such marked effects on the germinal components of the testis (growth of the seminiferous tubules and their epithelium) as to cause a threefold weight increase in the testis without appreciable effect on the interstitial or Leydig tissue, reflected in the infantile seminal vesicles. These results gain importance when we remind ourselves that the outstanding result of the administration of all gonadotropic substances hitherto known to us† is to cause more significant enlargement of the accessory organs of reproduction than of the testes.

The preceding paper was devoted to the study of the effects on the reproductive system of hypophysectomized females of the same hypophyseal synergist employed here, of combinations in vitro of this substance with pregnancy-prolan, and of pregnancy-prolan alone. The effects of the same substances on hypophysectomized male rats will now be described. The methods were those employed in the previous paper with the single exception that the duration of injection was usually longer than that required in the female, varying from 10 to 45 days. All preparations were carefully

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†Smith, Engle and Tyndale (1) have recently reported effects strikingly similar to those herein recorded on administering menopause urine to hypophysectomized male rats. The data herein reported point to the hypophyseal origin of the substance present in menopause blood and urine.

standardized for their independent gonadotropic as well as their synergic action in normal immature females.

In attempting to analyze the separate and combined effects of these materials on hypophysectomized males, the problem was approached from two different angles. In the first place, an effort was made to prevent degenerative changes in the testis, i.e., *maintain* the preoperative condition, or even stimulate further growth, by starting therapy immediately after operation. Next, the attempt was made to *repair* the atrophic testis of the hypophysectomized rat.

Although the primary aim was to discover the effect of these substances on hypophysectomized animals, it was deemed important to determine their effect also in normal males. The first half of Table I is devoted to such tests. (These animals were littermate brothers of the hypophysectomized animals listed later in this table.) Three of the normal animals were sacrificed at the beginning of the experiment (actually at 38 days of age), and 3 at its conclusion (when 51 days of age), in order to determine the weights of testes and seminal vesicles and the presence or absence of spermatozoa in the epididymis in animals at these ages uninfluenced by any agent. It will be seen that in the few days representing the duration of the experiment, the testes of normal animals doubled in weight and the seminal vesicles increased to approximately 5 times their former weight, and that spermatozoa appeared in the epididymis. It will be equally clear from the table that the testes of these normal animals were not appreciably influenced in weight by the administration of either of the 2 substances employed in these experiments, or by their combination. Although both pregnancy-prolan and its combination with the hypophyseal synergist caused the seminal vesicles to increase from 4 to 6 times in weight, the hypophyseal synergist alone cannot be said to have appreciably influenced the development of the seminal vesicles. As will be seen later, this is in consonance with its lack of action on the seminal vesicles of hypophysectomized animals. The pronounced effects of the combination on the same structures, as well as the effects of prolan alone, clearly establish the capacity of the seminal vesicles at this age to respond easily and markedly to an appropriate hormonal stimulus.

MAINTENANCE OF TESTES AND SEMINAL VESICLES OF HYPOPHYSECTOMIZED RATS

Immature Males. Littermate brothers of the foregoing normal immature rats were hypophysectomized at the 38th day of life, and 2 days later daily treatment was inaugurated—the treatment consisting of a total of 10 daily subcutaneous injections of the hypophyseal synergist, pregnancy-prolan, or the combination of these substances in vitro, the animals being sacrificed on the 11th day. Although the recession which ensues in the sex organs of males after hypophysectomy at this epoch of life is well known, an untreated hypophysectomized animal was sacrificed at the end of the

experiment. As the second half of Table I will show, all 3 methods of treatment of the hypophysectomized animals favorably affected the testis weights. It appears, indeed, that the hypophyseal synergist and its combination with prolan enabled the testes of these hypophysectomized young males to maintain almost their normal rate of growth and differentiation. The pregnancy-prolan, when administered alone, did not maintain testes of equal weight, but marked influence on their growth was demonstrable, and as in the other two types of therapy, spermatozoa were found in the epididymis.

TABLE I

MAINTENANCE OF THE REPRODUCTIVE ORGANS OF IMMATURE NORMAL AND HYPOPHYSECTOMIZED MALE RATS BY ADMINISTRATION OF THE HYPOPHYSEAL SYNERGIST, OF PREGNANCY-PROLAN, AND COMBINATIONS THEREOF.

Type of Animal	Treatment		Age			Organ Weights at Autopsy		Spermatozoa in Epididymis
	Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy	Testes	Seminal Vesicles	
		Days	Days	Days	Days	mg.	mg.	
Normal	Hypophyseal Synergist[1]	10	—	40	51	1970	112	+
		10	—	40	51	2110	149	+
		10	—	40	51	1990	142	+
"	Pregnancy-Prolan[2]	10	—	40	51	2110	660	+
		10	—	40	51	2140	790	+
		10	—	40	51	1890	432	+
"	Combination	10	—	40	51	2110	410	+
		10	—	40	51	1910	406	+
		10	—	40	51	2490	590	+
"	Untreated	—	—	—	38	893	22	−
		—	—	—	38	935	22	−
		—	—	—	38	869	30	−
		—	—	—	51	2090	100	+
		—	—	—	51	2010	97	+
		—	—	—	51	1790	121	+
Hypophysectomized	Hypophyseal Synergist[1]	10	38	40	51	1720	25	+
		10	38	40	51	1390	21	−
		10	38	40	51	1840	36	+
		10	38	40	51	1050	24	
"	Pregnancy-Prolan[2]	10	38	40	51	990	370	+
		10	38	40	51	1420	291	+
		10	38	40	51	1020	308	+
"	Combination	10	38	40	51	1490	500	+
		10	38	40	51	1810	381	+
		10	38	40	51	1470	400	−
		10	38	40	51	1890	479	+
"	Untreated	—	38	—	51	390	17	−

1. The hypophyseal synergist (W1753) was a 40% alcoholic extract of desiccated sheep hypophyses, given in a total dose per rat of 9.1 mg. The standarization of the synergist in immature female rats is as follows: synergist 2.7 mg., ovaries 32 mg., prolan 6.8 mg., ovaries 38 mg.; combination, ovaries 100 mg., activation 92%; antagonism (hypophyseal fraction intraperitoneal, prolan subcutaneous), ovaries 30 mg. This is the same hypophyseal preparation injected into 23-day-old hypophysectomized females. (See preceding paper, Table II, W1735.)

2. The prolan used was an alcohol precipitate from urine of pregnant women and was given in a total dose per rat of 22.7 mg.

The findings as regards the seminal vesicles were interesting in the extreme. These were uninfluenced in males treated with the hypophyseal synergist, remaining in infantile condition. In contrast to this result they had increased some tenfold in the group treated with pregnancy-prolan

(where they were 3 times the weight of seminal vesicles of normal animals at this age) and had increased thirteenfold in the group treated with the combination.

Histological study was made of the testes of the immature hypophysectomized animals submitted to the 3 types of treatment. It showed that the maintenance of approximately normal testis weights in all 3 groups was associated with testicular tubules of approximately normal diameter and normally differentiated seminiferous epithelium (Figs. 4, 5 and 6). The development attained by normal untreated littermates at this time is shown in Figure 3. The degree of atrophy present in the testes in untreated hypophysectomized animals at this interval after operation (13 days) is shown in Figure 2. The development of the testis at time of operation is shown in Figure 1. Besides showing the maintenance and development of the testes Figures 4, 5, 6 also show that an increase in the interstitial tissue has occurred in the prolan and combination-treated animals, an effect correlated with the marked growth of the seminal vesicles seen in these groups.

REPAIR OF TESTES AND SEMINAL VESICLES AFTER VARIOUS PERIODS OF REGRESSION

While the preceding experiments indicate that maintenance of normal testis weight and structure can be approximated if treatment is begun promptly after hypophysectomy, a more crucial test of the value of the 3 methods of treatment as employed for actual substitution therapy would come from the study of their capacity to repair or reinstate seriously degenerated gonads. Consequently other males were hypophysectomized and time was allowed for regression of the sex organs to ensue before therapy was begun. Two series of experiments were made: the first with a group of animals 23 to 24 days old at operation in which 6 days were allowed for regression, the other with a group of animals 34 to 40 days old when hypophysectomized in which 15 to 20 days were allowed for regression. In both these groups one testis was removed at the onset of injection, so that in the case of each individual the testicular weight and structure at the beginning of therapy was known.

Table II summarizes the results obtained from injection of 23- to 24-day-old males with hypophyseal extract containing the synergist, with pregnancy-prolan, and with the combination thereof. It will be noted that after a 6-day period of regression the average weight of the testis was half the weight at the age of operation (65 mg. as compared with 136 mg.). After the 11-day period of injection, the remaining testis of rats treated with the hypophyseal synergist had increased two to threefold in weight, and in the group treated with the combination three to fourfold. The weight of the testis of the rats injected with pregnancy-prolan alone, however, showed, with but 2 exceptions, no significant increase above that of the control testis removed at the onset of injection. It would appear that very young animals are less sensitive to pregnancy-prolan. Whereas the seminal vesicles of the

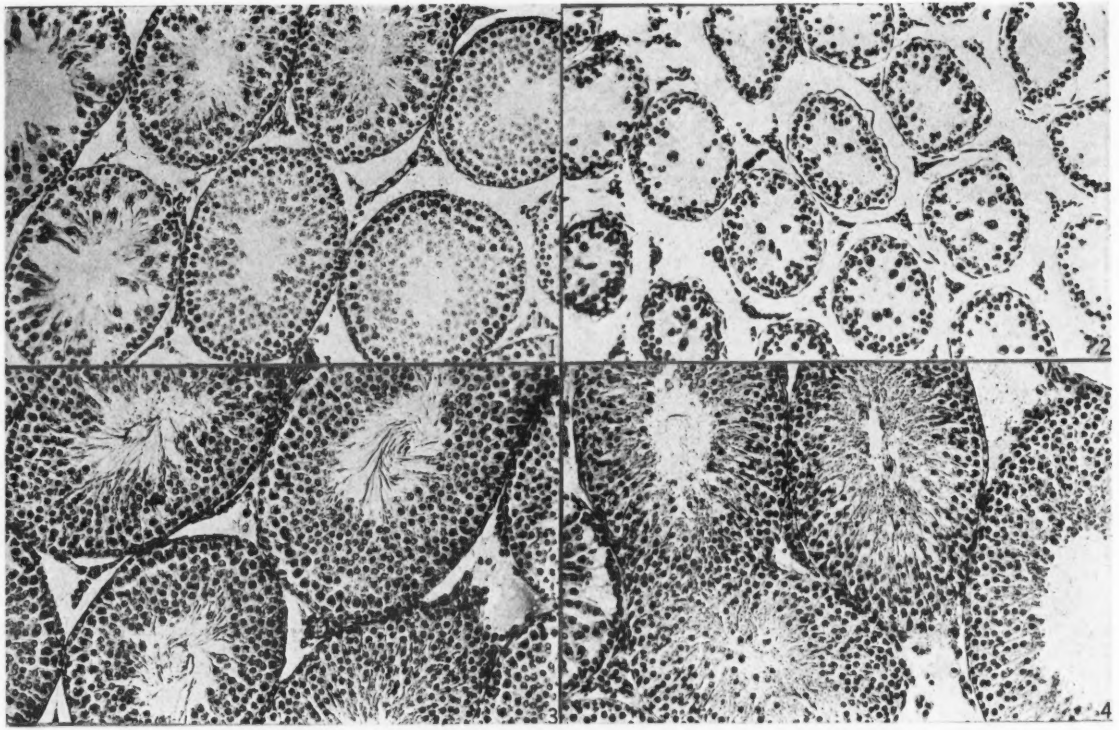

PLATE I

Figure 1. Small area through testis of a normal rat at 38 days of age. x145.
Figure 2. A similar area through the testis of a littermate control hypophysectomized at 38 days of age and necropsied 13 days later. Note degenerative changes. x145.
Figure 3. Section through testis of a normal rat at 51 days of age. x145.
Figure 4. Section through testis of an hypophysectomized rat (38 days old at the time of operation) treated for 10 days with an hypophyseal extract containing the synergist. Injections begun 2 days after the operation. Note that spermatozoa are present. Note that the diameter of the tubules are approximately the same as that of the normal control (Figure 3) of the same age. x145.

TABLE II

ATTEMPTED REPAIR OF THE REPRODUCTIVE ORGANS OF IMMATURE HYPOPHYSECTOMIZED MALE RATS AFTER 6 DAYS OF REGRESSION BY ADMINISTRATION OF THE HYPOPHYSEAL SYNERGIST, OF PREGNANCY-PROLAN AND OF COMBINATIONS THEREOF.

Treatment		Age			Organ Weights			Spermatozoa in Epididymis
						At Autopsy		
Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy	Testis at Onset of Injection	Testis	Seminal Vesicles	
	Days	Days	Days	Days	mg.	mg.	mg.	
Hypophyseal Synergist[1]	11	24	30	41	57	162	10	–
	11	24	30	41	66	181	—	–
	11	23	29	40	66	176	8	–
	11	24	30	41	58	174	8	–
	11	24	30	41	68	209	6	–
	7	23	30	36	53	99	8	–
Pregnancy-Prolan[2]	11	23	29	40	56	77	34	–
	11	24	30	41	68	116	23	–
	11	23	29	40	62	97	15	–
	7	24	30	36	73	73	20	–
	9	24	30	38	62	76	27	–
Combination	11	24	30	41	59	239	56	–
	11	24	30	41	70	282	—	–
	11	24	30	41	74	225	50	–
	11	24	30	41	63	193	22	–
	11	23	29	40	60	242	36	–
	9	23	29	37	65	145	27	–
Untreated (Hypophysectomized Control)	—	23	—	30	—	58	8	–
Untreated (Normal Controls)	—	—	—	24	—	159	11	–
	—	—	—	24	—	132	10	–
	—	—	—	24	—	119	10	–
	—	—	—	41	—	605	38	–
	—	—	—	41	—	350	19	–
	—	—	—	41	—	570	24	–

1. The hypophyseal synergist (W2065) was prepared by trypsin digestion of an alkaline extract of pig pituitary given in a total dose of 10 mg. in 11 injections. The standardization in immature females is as follows: synergist 2.7 mg., ovaries 28 mg.; prolan 6.8 mg., ovaries 25 mg.; combination, ovaries 93 mg., activation 165%; antagonism (hypophyseal fraction intraperitoneal, prolan subcutaneous), ovaries 22 mg.

2. The prolan used was an alcohol precipitate from urine of pregnant women and was given in a total dose of 22.7 mg. in 10 injections during 11 days.

animals treated with the hypophyseal synergist remained completely unaffected, the seminal vesicles of the groups receiving pregnancy-prolan and the combination of these substances showed a very considerable increase in weight.

The tubules were definitely enlarged in all groups (synergist, prolan, combination), least in the animals injected with prolan, and most in those receiving the combination. Development in no case had passed the spermatocyte stage. Giant cells had decreased in number. While no increase of interstitial tissue occurred in the groups receiving the synergist, the interstitial tissue was definitely increased in the groups receiving prolan and the combination, perhaps more in the latter group. In both the groups receiving prolan and the combination, the interstitial tissue was even greater in amount than in normal controls sacrificed at the time of operation.

More successful repair was attained in slightly older animals (35 to

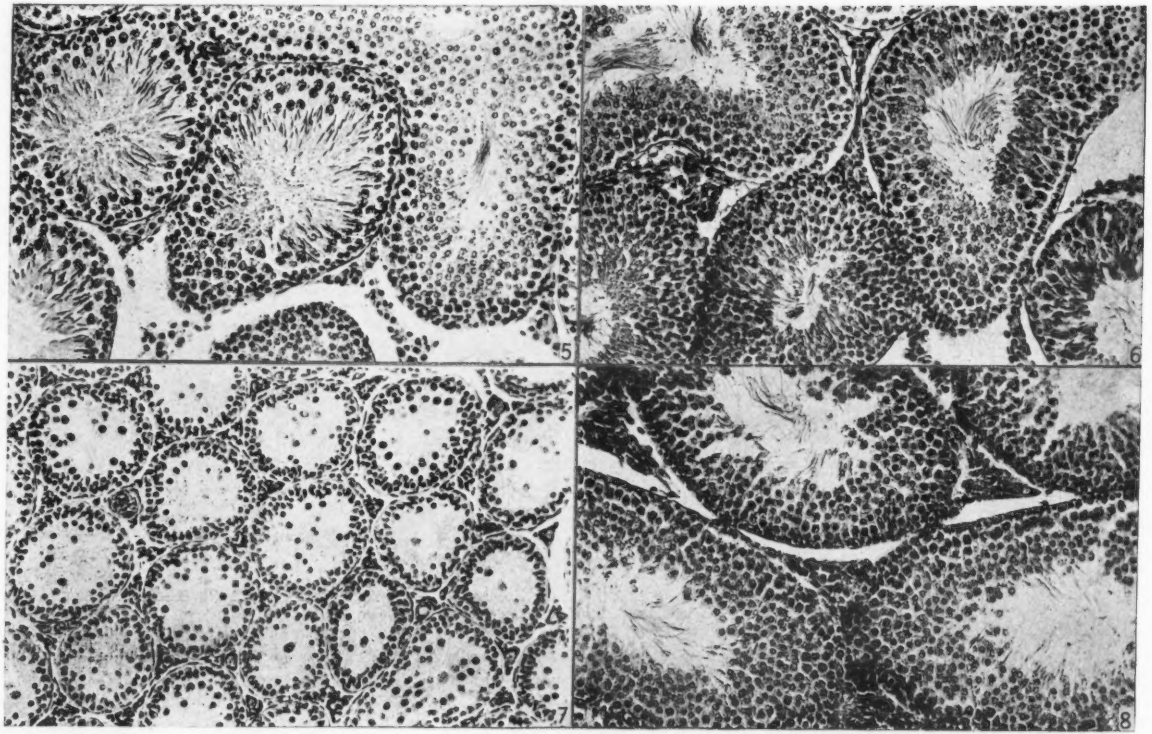

PLATE II

Figure 5. Section through testis of an hypophysectomized rat treated for 10 days with pregnancy-prolan (38 days old at hypophysectomy). Treatment begun 2 days after the operation. Note increase of interstitial tissue and abundance of spermatozoa. x145.

Figure 6. A similar section through testis of an hypophysectomized littermate to the above, treated with the combination of pregnancy-prolan and the hypophyseal synergist. Age at operation and duration of treatment same as above. x145.

Figure 7. Section through the left testis of a rat hypophysectomized at 40 days of age to show the degenerative changes after an interval of 20 days. x145.

Figure 8. A corresponding section through the right testis of the same animal (Figure 7) after a 25-day treatment with the in vitro combination of pregnancy-prolan and hypophyseal synergist. Note the marked increase in the diameter of the tubules, abundance of spermatozoa and restoration of the interstitial tissue. x145.

40 days old at hypophysectomy) even though the period between operation and onset of injection was longer than in the preceding case (15 to 20 days). The results are given in Table III. It will be seen that with all 3 types of therapy the weight of the testis at the end of the injection period exceeded that at the onset of injection, being usually 2 to 3 times the original size, and even being increased fivefold after injection for 25 days with the combination. The testes of animals which had received the synergist, when examined under the microscope, showed an enlargement of the tubules, an increase in the number of germinal layers, and many mitotic figures, but

TABLE III

ATTEMPTED REPAIR OF THE REPRODUCTIVE ORGANS OF IMMATURE HYPOPHYSECTOMIZED MALE RATS AFTER 15-20 DAYS OF REGRESSION BY ADMINISTRATION OF THE HYPOPHYSEAL SYNERGIST, OF PREGNANCY-PROLAN AND OF COMBINATIONS THEREOF.

Treatment		Age			Organ Weights			Spermatozoa in Epididymis
						At Autopsy		
Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy	Testis at Onset of Injection	Testis	Seminal Vesicles	
	Days	Days	Days	Days	mg.	mg.	mg.	
Hypophyseal Synergist[1]	15	40	55	70	179	354	26	–
	20	37	55	75	134	409	11	–
	30	35	55	85	75	368	11	–
	45	40	55	100	150	276	13	–
Pregnancy-Prolan[2]	23	34	55	78	102	269	216	–
	30	39	56	86	180	394	71	–
	45	39	56	101	141	292	135	+
Combination	10	40	60	70	101	245	19	–
	15	36	55	70	112	375	61	–
	25	40	60	85	129	664	367	+
Untreated (Hypophysectomized Controls)	—	36	—	56	—	113	17	–
	—	36	—	56	—	177	20	–
Untreated (Normal Controls)	—	—	—	35	—	587	36	–
	—	—	—	35	—	515	24	–
	—	—	—	40	—	676	48	–
	—	—	—	39	—	529	35	–
	—	—	—	40	—	612	46	–
	—	—	—	50	—	597	41	–
	—	—	—	60	—	1232	68	+
	—	—	—	101	—	1417	325	+

1. The hypophyseal synergist (853) was a 40% alcohol extract of pig pituitary given in a daily dose of 0.45 mg. Injections were continued for varying intervals, always until the time of autopsy.

2. The prolan used was a simple alcohol precipitate from urine of pregnant women, given in a daily dose of 0.91 mg.

the interstitial tissue was uninfluenced. Spermatids, though few in number, were found in many of the tubules. This picture stood in marked contrast to the one presented by the degenerated testis removed at the onset of injection in which the tubules contained only 2 to 3 cell layers, many giant cells, and no differentiation beyond the spermatocyte stage.

It is to be especially noted that the seminal vesicles remained infantile, not weighing more than those of the hypophysectomized controls, although the testes were approximately doubled in weight as a result of the injection.

The atrophic seminal vesicles mirrored the almost complete lack of interstitial tissue seen in the testes of the group.

The testicular tubules of animals treated with prolan also showed marked reparative phenomena. The tubules were enlarged and many mitotic figures were present. Spermatids were found in 2 of 3 animals in the group and in the third animal, treated for 45 days, spermatozoa were present in the tubules and in the epididymis. The seminal vesicles were markedly enlarged in all animals receiving prolan and there was an evident increase in the interstitial tissue of the testis. The greater development of interstitial tissue in this group was the most outstanding difference in testicular structure which distinguished them from the synergist treated group.

These results obtained with pregnancy-prolan are contrary to the reports of Collip and his colleagues (2), who found no effect on the tubules of hypophysectomized male rats, but are in accord with the recent experiments of Smith and Leonard (3).

The injection of the combination of prolan and the synergist also gave striking increases in both testicular and seminal vesicle weights in those cases in which the injections were continued for 15 days or more. One animal injected for only a 10-day interval showed a decided increase in the size of the testicles, but no change in the seminal vesicles, the latter retaining their infantile condition. After 15 days' treatment, the testis of one animal had increased threefold in weight and after 25 days' injection in another case over fivefold in weight. The weight of the testis of the animal treated for 25 days with the combination of prolan and synergist equalled that of a normal control animal sacrificed at the time of operation, but was far below the weight of the testis of a normal animal sacrificed at the end of the injection. Sperm was found in the epididymis and in the testicular tubules of this animal. This is shown in Figure 8; Figure 7 shows the atrophic condition of the testis at the onset of therapy. In this animal, the seminal vesicles had attained a weight of 367 mg. This is to be compared with a weight of 48 mg. normal for the age at which the operation was performed. These seminal vesicles actually equalled in weight those of a normal animal of the same age. The seminal vesicles of the 2 untreated hypophysectomized control rats sacrificed at this age had become reduced to 17 and 20 mg., respectively.

It has already been shown that the seminal vesicles of young hypophysectomized animals do not develop on injection of the hypophyseal synergist alone. It would therefore be of interest to see if conversely the seminal vesicles of animals hypophysectomized after maturity had been reached would undergo the usual regression after hypophysectomy if injections of synergist were begun immediately after hypophysectomy. This procedure was followed in the experiments reported in Table IV. These animals were 86 to 98 days of age at operation. Injections were begun within 48 to 72 hours after operation and to make the test more conclusive were continued

for 20 days. The seminal vesicles did undergo marked atrophy during this period though they did not recede so rapidly as did those of the hypophysectomized littermates. The testes of these injected animals were undoubtedly maintained and living spermatozoa were still found in the epididymis at autopsy, although sperm were not encountered in the epididymis of the untreated hypophysectomized controls after this interval.

There is no suitable explanation for this appreciable though slight retardation of the atrophy of the accessories when the synergist is administered to hypophysectomized adults. It is possible that the slowed regression of adult seminal vesicles observed here might be due to the presence of small amounts of gonad-stimulating hormone in the hypophyseal preparation. On the other hand, the testis and seminal vesicles once matured may behave differently toward the hypophyseal synergist because of the

TABLE IV

ATTEMPTED MAINTENANCE OF THE REPRODUCTIVE ORGANS OF MATURE HYPOPHYSECTOMIZED MALE RATS BY ADMINISTRATION OF THE HYPOPHYSEAL SYNERGIST.

Treatment		Age			Organ Weights at Autopsy		Spermatozoa in Epididymis
Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy	Testes	Seminal Vesicles	
	Days	Days	Days	Days	mg.	mg.	
Untreated (Normal Controls)	—	—	—	86	2790	815	+
	—	—	—	109	2780	970	+
	—	—	—	109	3601	1180	+
Untreated (Hypophysectomized Controls)	—	86	—	93	1190	182	+(not motile)
	—	86	—	109	710	100	−
	—	98	—	113	1385	147	−
	—	98	—	113	950	148	−
Hypophyseal Synergist[1]	20	98	100	120	1590	287	+
	20	86	89	109	1960	171	+
	20	86	89	109	2930	680	+
	20	86	89	109	2380	240	+

1. The hypophyseal preparation (W2028) used was a 40% alcohol extract of sheep anterior pituitary and was given in a total dose of 15 mg. per rat in 20 days. The standardization in immature female rats was as follows: synergist 1.3 mg., ovaries 18 mg.; prolan 27.3 mg., ovaries 31 mg.; combination, ovaries 115 mg., activation 271%; antagonism, (synergist intraperitoneal, prolan subcutaneous), ovaries 16 mg.

persistence of already developed interstitial tissue. A more drastic and hence more convincing test of the effect of the synergic substance on seminal vesicles of hypophysectomized rats would therefore be afforded by the injection of hypophysectomized mature animals after a long postoperative pause, one certain to lead to profound atrophy of the reproductive system. Table V shows that when a pause of 40 days was enjoined after hypophysectomy of 84 to 90-day-old males, and 20 daily injections of the synergist were given, a threefold increase of testis weights occurred and that no effect whatever on the seminal vesicles resulted. This experience was convincing as regards the differential effect of the synergic substance.

It is to be pointed out, of course, that in none of the experiments herein reported can the claim be made that a complete separation has been

affected in the hypophyseal substance stimulating the seminiferous tubules as distinguished from that stimulating the interstitial tissue and hence accessory apparatus. It can only be said that at the dose levels and for the time intervals employed, hypophyseal extracts can be made which clearly stimulate the seminiferous components of the gonads more than they affect the interstitial components and accessory organs.

TABLE V

ATTEMPTED REPAIR OF THE REPRODUCTIVE ORGANS OF MATURE HYPOPHYSECTOMIZED MALE RATS AFTER 40 DAYS OF REGRESSION BY ADMINISTRATION OF THE HYPOPHYSEAL SYNERGIST.

Treatment		Age			Organ Weights				Spermatozoa in Epididymis
					At Onset of Injec.		At Autopsy		
Solution	Duration	At Hypophysectomy	At Onset of Injection	At Autopsy	Testis	Seminal Vesicle,	Testis	Seminal Vesicle,	
	Days	Days	Days	Days	mg.	mg.	mg.	mg.	
Hypophyseal Synergist[1]	20	90	130	150	276	36	610	48	–
	20	90	130	150	193	42	540	38	–
	20	84	124	144	259	31	590	31	–

1. The hypophyseal preparation (W2028) is the same as that used in maintenance experiments on adult males (Table IV).

SUMMARY

The contrasting effects of pregnancy-prolan and prolan combined with the hypophyseal synergist on hypophysectomized female rats have been described in the preceding paper. Here interest has centered on the effects of these gonadotropic substances on hypophysectomized male rats.

The testes of male hypophysectomized rats (24 to 90 days old) treated immediately after the operation for 10 to 20 days with an hypophyseal synergist, pregnancy-prolan or a combination thereof were maintained or caused to grow beyond their operative weights. The testes of animals receiving the hypophyseal synergist and the combination were brought within the weight range of these organs in normal animals of this age. Spermatozoa were produced in the testes of animals under all 3 types of treatment. Similarly, repair of the testicular tubular epithelium was possible in hypophysectomized rats after a period of 40 days had intervened between hypophysectomy and the onset of injections.

When administered alone, the hypophyseal synergist though thus causing marked repair of the seminiferous tubules left the interstitial tissue and the seminal vesicles unaffected—the latter remaining infantile. On the other hand, prolan produced an increase in the Leydig tissue and a rapid repair and development of the seminal vesicles and it is to be noted that its combination with the hypophyseal synergist caused a still greater development of the accessories.

The foregoing experimental results, which have been repeatedly secured (on a total of 85 rats, 53 of which were hypophysectomized) appear to amply justify the statement that a separation has been effected as regards anterior hypophyseal gonadotropic substances—into those stimulating the

production of the male germ cells (gametogenetic activity) and those stimulating the production of the male sex hormone (testicular endocrine activity).

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HORMONES OF THE HYPOPHYSIS OF THE INFANTILE RAT

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Attempts to differentiate the hormones of the hypophysis have resulted in much confusion, but recent work indicates that this is due largely, if not altogether, to the choice of animals used when testing the hormones affecting the ovary. Reichert, et al. (1932), have shown that prolan is ineffective in the hypophysectomized rat and dog in producing ovarian stimulation, no follicular growth taking place. Noguchi (1931), Collip, et al. (1933), and Leonard and Smith (1933) have shown that human pregnancy urine and blood serum, as well as placental extracts, produce no follicular growth in hypophysectomized rats but do produce luteal cells from the thecal cells. Many investigators have established the fact that these same extracts, when used in normal immature rats, will induce the formation of ovaries heavier than those of adults. Comparing these two sets of data, it seems unquestionable that these preparations alone are not able to cause follicular growth, and that that which occurs following their administration to normal rats is due to an activation factor (1), present during pregnancy, which stimulates the hypophysis of the host; hence the lack of such effects in the hypophysectomized animal.

In all experiments on the normal animal these results must be given due consideration. The efficacy of the preparations to be tested in stimulating the animal's own hypophysis to greater activity must be known before any conclusions can be drawn regarding the component hormones of the preparations. The attempts to differentiate a follicular-growth from a luteinizing hormone illustrate this point. The work cited above, showing that human pregnancy extracts will produce lutein cells but not follicular growth in hypophysectomized animals, seems good evidence that these two phases of ovarian development are produced by different hormones. Other investigators have used the normal animal for testing these extracts and have found that both luteinization and follicular growth occur in most cases, a result to be expected with the animal's own hypophysis responding to the activator in the extracts.

Evans, et al. (1932), were the first to suggest the possibility of prolan being an activator of some element of the hypophysis of the host.

(1) It is apparently the presence of this activation factor in the urine of pregnancy which makes possible the Aschheim-Zondek test, and not the hypophysial hormones. To date only two hormones have been shown to occur in the extracts of human pregnancy blood, urine, and placenta, a luteinizing hormone and this activation factor. While the former seems to be identical with that from the hypophysis, and may possibly be derived from it, it seems likely that the latter is a placental product. The work of Evans *et al* (1933) indicates that mare serum is a different product, 6.5 R. U. of prolan for 25 days inducing ovaries weighing 28 mg., while 4 R. U. of mare serum for 30 days resulted in ovaries weighing 188 mg. in the hypophysectomized rat.

It has been shown that there are no evidences of the activity of the maturity hormone (follicular-growth plus luteinizing hormones) in the ovary of the rat before about the eighteenth day (Swezy, 1933). It is well known that precocious ovarian development cannot be induced before this time, either by stimulation of the rat's own hypophysis or by the administration of hypophysial hormones. The work of Smith and Engle (1927) and Smith and Dortzbach (1929), producing maturity hormone effects by the implantation of hypophyses of rats five days old and those of foetal pigs into immature rats and mice of suitable age, shows that these infantile hypophyses possess the power to induce maturity hormone effects in older rats, though they cannot be themselves stimulated. Other investigators have noted that the hypophyses of immature animals produce maturity hormone effects when used as implants, while *in situ* they produce only growth hormone effects. Whether the action of the hypophysis of the immature rat is similar to that of the mature one can only be tested in the hypophysectomized animal. Such tests show a lack of similarity, as the following results indicate. These experiments were carried out with the aid of Miss Morvyth McQueen-Williams, whose careful and efficient work is gratefully acknowledged.

Male rats were used as both donors and recipients. More extensive work with female rats will be reported by Miss McQueen-Williams. Mature rats had been hypophysectomized from 37 to 101 days before treatment began. The loss of weight and general condition of the rats, particularly the small size of the genital organs, gave evidences of complete removal of the hypophysis. The donors were male rats ranging from one to 21 days. The hypophyses of these were not weighed before being used, but the values were computed from Donaldson's tables (1924), hence may not be quite exact for this particular strain of rats. The weights of the hypophyses of the adults are those established by the work of Evans.

Three types of controls were used, hypophysectomized untreated rats, hypophysectomized rats treated with tissue from adult donors, and immature rats treated with both immature and adult hypophyses. Immature untreated rats were also used as controls for the latter group. It was found that a total dosage of one and one-half hypophyses, about 12 to 13 mg., from adult donors gave a noticeable effect on the seminal vesicles and external genitals, and the amount of tissue from young rats was kept near this level. With the one-day rats the tissue was implanted in one, two, or three doses; with the others, on three successive days. Autopsy or removal of the gonads (some rats were kept for other experimental purposes) occurred on the sixth day. The results are given in Table 1.

There were no evidences of changes in either the seminal vesicles or in the scrotum of the hypophysectomized rats receiving hypophyses from rats one to 13 days old. The increase in body weight (not recorded here) during the time of treatment shows that these implants were releasing hormones into the circulation, so that the lack of maturity hormone effects

TABLE 1

SHOWING THE EFFECTS OF IMPLANTING HYPOPHYSES OF IMMATURE RATS INTO HYPOPHYSECTOMIZED ADULT RATS, ALL MALES

Number of Rats	Donor	Implants		Seminal Vesicles mg.	Testes mg.	External Genitals
		Number	Weight, mg.			
Hypophysectomized 37 to 101 days						
9	Controls.....	....	....	76	443	
2	1 day.....	64.	32.6	68	407	No effect.
1	1 day.....	82.	41.8	78	456	No effect
3	5 days.....	18.	14.6	78	560	No effect.
2	10–13 days...	15.	18.0	66	612	No effect
1	21 days.....	8.	12.0	166	700	Descent of testes.
1	21 days.....	6.	9.0	154	720	Complete descent.
2	Adult.....	1.5	13.0	107	650	Noticeable descent.
1	cast.....	1.	12.0	115	750	Noticeable descent
21 and 24 day controls						
1	1 day.....	36.	18.0	6	304	No effect.
2	1 day.....	64.	32.0	10	293	Sac pink and firm.
1	21 days.....	5.	7.5	10	300	Sac pink and firm.
2	Adult.....	1.5	13.0	10.5	288	Larger than controls.
1	Cast.....	1.	12.0	25	595	Sac large and pink.
1	Adult.....	2.	17.6	9	320	Sac enlarged.
5	Untreated....	....	....	3.3	342	

could not be due to an unsuccessful "take," but seems to be due to a lack of maturity hormone in the tissue. In the rat of 21 days hypophyses from rats of one day show typical maturity effects similar to those given by adult hypophyses.

The most striking effects on the hypophysectomized rats are found with implants of 21-day hypophyses, these giving larger seminal vesicles than those from normal adults. The number of rats is small but the work of others indicates that the hypophysis of the rat near this age has a greater potency than that of an adult. Evans and Simpson (1929, a, b) reported that four 24-day-old male rat hypophyses induced the formation of ovaries averaging 41 mg. in young rats, while four adult male rat hypophyses gave ovaries averaging 70 mg., and four castrated males an average of 176 mg. Comparing the amount of increased weight with the weight of tissue implanted, it is found that the hypophysis of the male rat of 24 days is as potent as that of the castrated adult male, and more than twice as potent

TABLE 2

COMPARISONS OF OVARIAN WEIGHTS, PER UNIT WEIGHT OF IMPLANTS, INDUCED BY HYPOPHYSES OF 24-DAY AND ADULT RATS (FROM EVANS AND SIMPSON, 1929A, B). WEIGHT OF CONTROL OVARIES 17 MG.

Number of Rats	Number of Implants	Weight of Implants mgm.	Average Weight Ovaries mgm.	Increase in Weight mgm.	Increased Weight Per Unit of Implants* mgm.
3	4–24 day ♂	7.2	41.0	24.0	3.39
34	4 ♀	47.6	19.7	2.7	0.06
12	4 ♂	34.4	70.0	53.0	1.51
6	4 cast. ♀	49.3	113.5	96.5	1.94
6	4 cast. ♂	48.8	176.0	159.0	3.25
3	6–2 day ♂	10.8	60.0	43.0	3.98
6	6 ♀	69.6	29.0	12.0	0.17

*Figures in this column were obtained by dividing the increase in weight by the number of milligrams implanted.

as the normal adult, with corresponding values for the female, as may be seen in Table 2. This agrees with and explains our results (2).

DISCUSSION

The results of these experiments seem to establish the conclusion that the hypophysis of the rat does not produce appreciable amounts of sex hormones during early post-natal life. It has been demonstrated by Smith and Engle and confirmed by this work, that the hypophyses of rats of these early ages will induce maturity hormone effects when used as implants in rats 21 days or older. This would suggest that a factor is present in the hypophysis during this period which is able to stimulate the hypophysis of an older rat, this resulting in all the characteristic features of ovarian stimulation shown by more mature hypophyses (3). These hormones are normally present in amounts sufficient to cause an increase in the size of follicles in the ovary beginning about the eighteenth day. Before this time the follicles do not normally attain a size greater than may be found in the hypophysectomized rat. The administration of even large amounts of hormones will not induce complete follicular growth before about the twentieth day. This date seems to be a crucial one for the hypophysis of the rat, and marks the time when it normally begins to produce the follicular-growth hormone and when it may be stimulated, for the first time, to produce the other hormones which, acting on the ovary, result in the formation of mature follicles, ovulation, and luteinization. That they cannot be evoked before this time would seem to be due to an incapacity on the part of the hypophysis to produce them.

In striking contrast to the apparently slight changes normally occurring at this time in the hypophysis-ovary relations, is the remarkable fact that the hypophysis of the rat 21 to 24 days old has a greater potency, per unit of weight, than adult hypophyses when implanted into normal and hypophysectomized rats. Since this effect is found in the latter it cannot be due to an activator, as might be claimed for the rat with hypophysis intact. From a lack of hormone effects at day 13 there is a sudden sweep upward, bringing the hypophysis to its fullest potency at day 21, a potency which can be revealed only by introducing the hypophysis into another host. There can be no relation between this high potency and somatic maturity of the host, since it is found with the 21-day-old host also.

The similarity between the potency of the hypophysis in the rat 21 to 24 days old and that of the castrated adult, at once suggests the operation of the same factor in both cases, a total lack of hormones from the gonads, since these have a restraining influence on the hypophysis. In the ovary of

(2) On the eve of sending this to the press, the report of Lipschütz (Endokrinologie, **31**: 90. 1933.) was received, in which he states that the coefficient of the luteinizing efficacy of hypophysial implants of immature female rats was 1.2-4.0, that of adult females, 0.0-0.03, and castrated females, 2.3. These results are similar to those in the male rats, noted above.

(3) The statement that the secretion of a gland cannot react upon the gland itself, seems to be contradicted by this evident stimulation of the hypophysis of the host by that from another rat. Both in the case of the hypophysis of the rat of one day and of 21 days into 21 day rats, this stimulation may be a nullification of an inhibiting factor, and thus only secondarily a reaction on the hypophysis itself.

the rat, follicles of medium-large size are not produced until about day 30, and those of mature size somewhat later. The size of the follicles seems to be directly correlated with the amount of folliculin produced. There is some evidence, from work being carried on by Miss McQueen-Williams, that the high potency found at day 27 is lowered as early as day 35 in the female rat, evidence which agrees with our conclusion that this potency is correlated with the amount of sex hormone produced by the ovary.

The small size of the follicles present in the ovary of the rat at days 21 to 24 offers a sharp contrast to the high potency of the hypophysis at this time, and would seem to be due to some inhibiting factor which holds the latter in check. It has been shown that some factor associated with the growth hormone, if not the growth hormone itself, may have an inhibiting effect on the hypophysis when given for long periods, even to the extent of inducing ovaries of the type found after hypophysectomy (Swezy, 1933). It may well be that it is the operation of such a factor which prevents the hypophysis from exerting its full influence on the ovaries of these infantile rats. This explanation seems more plausible than others that might be advanced.

During foetal and early post-natal life the sex hormones seem to have no effect on the gonads, even with large dosage. The administration of eight rat hypophyses daily for five days, during the latter part of pregnancy, had no effects on the gonads of the foetuses, even when this was supplemented by the implantation of one rat hypophysis daily in the young rat after birth (Swezy and Evans, 1931). Corey (1930) administered the pituitary extracts directly to the foetuses, with no results on the gonads of either sex. It is also significant that pregnancy is associated with an increased amount of maturity hormone, with no visible effects on the gonads of either sex. An even greater significance is attached to the fact that the ovary of the hypophysectomized rat presents the morphological features of the ovary during early immaturity, including a high rate of ovogenesis and the growth of small follicles (Swezy and Pencharz, 1933; Swezy, 1933). Burns and Buyse (1932) found that the gonads of hypophysectomized salamanders retained a stage of development equal to that of early immaturity. It would seem, therefore, that the early development of the gonad takes place independently of the hypophysial hormones, constituting its vegetative growth period determined by forces inherent in the organism itself, the sex hormones coming into play only when the reproductive period is approached.

It seems probable that the maturity hormone effects produced by Smith and Dortzbach with implants of hypophyses of foetal pigs into normal mice, was due to an activator in the foetal hypophysis, as in the case of the rat at the time of birth. There are no evidences that this activation factor is the maturity hormone nor can it be identified with any other known hormone of the hypophysis, and may possibly be the same factor reported by Evans, et al. (1933), in extracts of adult sheep and beef hy-

pophyses. Since its action is specific, the question of whether this constitutes another hormone of the hypophysis is a pertinent one.

SUMMARY

Hypophyses from male rats, ranging from one to 21 days, were implanted into hypophysectomized, adult, male rats on three successive days, with autopsy on the sixth day. Hypophysectomized and 21-day normal male rats were used as controls. Hypophyses from rats one to 13 days old gave no appreciable effects on the external genitals or the weight of the seminal vesicles, though those from rats one day old produced effects equal to those from adult male hypophyses in the 21-day controls. The hypophysis thus seems to contain no maturity hormone during this period, but does contain a factor which is able to stimulate the hypophysis of a normal rat of 21 days, or older, to precocious hormone production. Both in the hypophysectomized and in the 21-day controls, the hypophyses from rats 21 days old produced greater effects than were obtained from normal adults, per unit weight of tissue implanted. The hypophysis of the rat thus reaches its greatest potency at day 21, though this can be realized only by implanting it into another host.

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CONCERNING THE FUNCTION OF THE PINEAL BODY

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The stimulus to study experimentally the function of the pineal gland was given by clinical observations in patients with tumors of the pineal gland. Since these patients usually offered the most impressive picture of precocious puberty (pubertas praecox) or macrogenitosomia praecox, relations between pineal gland and sexual development were assumed to be most likely. The interpretation of the symptoms of precocious puberty found in cases of pineal tumors was based upon the assumption of either an hypopinealism due to destruction of pineal tissue by the tumor, or an hyperpinealism due to the stimulating effect of the tumor upon the glandular secretion.

Since the literature on this subject and the status of our present knowledge has been thoroughly reviewed and discussed in previous communications [Berblinger (1), Krabbe (2), Benda (3)], it is not intended to enter into further discussions, but to refer briefly to findings of previous authors relevant to the study reported here.

The assumption of a relationship between the pineal gland and sex glands was supported by the results obtained experimentally after pinealectomy. Increase in growth and weight of testis in young guinea pigs was observed by Horrax (4), similar results were obtained by Foa (5) in young fowls, and Demel (6) found increased testicular growth in rams. In contradiction to these findings, Dandy (7), as well as Kolmer and Loewy (8), were unable to note any testicular changes in young rats and dogs, respectively, after pinealectomy. Also, del Castillo (9), Weinberg and co-workers (10) did not observe any influence of pinealectomy upon the sex glands of young rodents.

EXPERIMENTAL STUDY

In view of these contradictory findings, it was contemplated to study the action of the human pineal gland upon the sexual cycle of female white mice by the method of implantation. Only adult white female mice were used for this experiment. The regular sexual cycle was previously determined by daily vaginal smears.

Three human pineal bodies (Table I), one of an adult man, one of an adult woman, and one of a female child, were implanted intramuscularly into the thigh

TABLE I

Pineal Body of	No. of Mice Implanted	Result
Adult Male	2	Sexual cycles undisturbed
Adult Female	2	
Child, Female	1	

of five female mice. All five animals made an uneventful recovery and daily vaginal smears taken thereafter did not show any change in their sexual cycle.

It was then thought necessary to ascertain whether or not the human pineal gland might exert some estrogenic activity upon castrated female white mice.

TABLE II

Pineal Body of	No. of Castrated Mice	Allen-Doisy Test
1. Male	2	Positive
2. Male (pineal body cystic)	2	Negative
3. Female	3	Positive
4. Male (sepsis)	2	Animals died
5. Female	3	Pro-estrus
6. Female	2	Pro-estrus
7. Male	2	Positive
8. Child	2	Pro-estrus
9. Male	2	Positive
10. Female	2	Positive
11. Female	3	Positive
12. Male	3	Positive
13. Male	3	Positive

Pineal bodies from individuals of various ages and sex (Table II) were equally divided and implaned by the same method into castrated mice. Estrus, as determined by a positive Allen-Doisy test, was produced by eight of thirteen pineal bodies after a period of from five to eight days after implantation. In three instances the Allen-Doisy test was not considered positive because the vaginal smear contained, in addition to numerous cornified epithelial cells, many epithelial cells which were still nucleated. One negatively reacting pineal body was found, on macroscopic examination before implantation, to be of cystic nature. One pineal body of a man, who died of septicemia and endocarditis, proved to be toxic for mice as both animals died shortly after implantation.

As the pineal bodies had been divided into 2-3 equal parts before implantation, it must be assumed that each positive reacting pineal body, the average weight of which is 150 mg., contained at least 2-3 mouse units of estrogenic substance.

Finally, it was considered important to ascertain whether, in addition to the estrogenic principle, the human pineal gland might contain the gonad-stimulating principle. In no instance did implantation of several pieces of human pineal gland into infantile female white mice, weighing 6-8 grams, result in ovarian stimulation such as folliculation, follicle hemorrhages, or luteinization.

DISCUSSION

The foregoing experiments may indicate that the human pineal body exerts an estrogenic influence upon the castrated mouse. This seems to be true, not only of the human pineal gland, but also, of the pineal gland of cattle and sheep with which Silberstein and Engel (11), in a very recent report (while this work was in progress), also were able to produce estrus in the castrated mouse.

In view of this estrogenic function of the pineal gland, the clinical picture of pubertas praecox in cases of pineal tumors would have to be explained on the basis of an increased glandular secretion due to the active stimulating effect of the tumor. This hyperpinealism then might be considered to be analogous to similar and better known conditions such as hyperparathyroidism, in cases of parathyroid tumors, and hyperinsulinism, in cases of tumors of the islands of Langerhans.

This theory, however, necessarily must be unsatisfactory to those observers according to whom the tumor has led to so much destruction of

the pineal gland that in serial sections no trace of pineal tissue was found. These authors believe that the normal pineal gland produces an inhibiting influence upon sexual development and that lack of this inhibiting influence, due to destruction of the organ by the tumor, leads to precocious puberty.

Although the findings, as stated above, would support the theory that the pineal gland exhibits an active stimulating effect on the sex development, a definite decision in favor of one or the other theory becomes exceedingly difficult in view of additional facts to be considered.

Aside from the fact that functional changes may be present in pineal glands which histologically appear normal, it must be kept in mind that the pineal form of pubertas praecox is but one manifestation of the disease, as suprarenal and gonad forms of the disease are known to exist. Furthermore, although aplasia of the pineal body, an extremely rare condition (12), has been found associated with gonadal atrophy, attention must be called to the possible existence of accessory pineal tissue. Kolmer and Loewy (8) have proved the existence of accessory pineal tissue in the pia-arachnoidea of dogs and long-tailed monkeys. Their findings, perhaps, may explain to some extent the various contradictory results obtained after pinealectomy.

As to the exact function of the human pineal body, it seems, therefore, that a definite statement cannot be made as yet, aside from a speculative hypothetic nature. Our findings, however, might be considered a further link toward the old conception that the pineal body plays a definite part in sexual development, the exact nature of which still remains unknown.

SUMMARY AND CONCLUSIONS

Experimental implantation of human pineal bodies was made into 36 white mice.

There was no inhibition of the sexual cycles of adult mice, and no gonadotropic influence in infantile mice was found.

The material, however, was capable of producing estrus in castrated mice, and each human pineal must have contained at least two to three mouse units of estrogenic substance. The significance of these findings, especially in relation to pubertas praecox, is briefly discussed.

The author wishes to express his indebtedness to Dr. Max Cutler, Director of the Tumor Clinic, and to Dr. Otto Saphir, Director of the Department of Pathology, for the liberal supply of human pineal bodies.

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THE NATURE OF THE GONADOTROPIC HORMONE FOUND IN THE URINE OF A CASE OF TERATOMA TESTIS

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The excretion of the gonadotropic hormones in human urine from other than pregnant individuals has been reported. Zondek (1930, 1931) has shown that castrated women, women past the menopause, and certain individuals with genital carcinomata excrete a particular gonadotropic hormone capable of stimulating only follicular development in the ovaries of immature rats and mice. Indeed, in the period of treatment (5 days), the ovaries of the infantile animals very rarely contain corpora lutea, yet these bodies and hemorrhagic follicles are present following pregnancy urine treatment.

Zondek (1931) has also reported that tumors of the testes will stimulate the secretion of the follicle-stimulating substance (prolan A) but that if very large doses are given, slight luteinization sometimes occurs. Weinstein and Schofield (1932) have reported a positive Friedman test with the urine from a case of teratoma testis. They induced ovulation in the rabbit with 24 cc. of urine, but this test alone gives no information on the nature of the gonadotropic hormone involved. We were likewise successful in producing ovulation in a rabbit with 15 cc. of urine from the case here reported, on two occasions. At other times the rabbit test was negative, although prolan was still being excreted. Recently, Ferguson (1933) presented an excellent account of the use of the Zondek test for diagnosing cases of teratoma testis. Neither does he make a clear distinction of the nature of the gonadotropic hormone, but designates the active principle as prolan A after Zondek.

It has been demonstrated that the gonadotropic substances found in the urine of castrated women (follicle-stimulator), as well as pregnancy urine, can induce ovulation in rabbits, but that these two substances do not have the same physiological effect on immature rat ovaries (Leonard, 1931). Further differences between these urinary hormones are observed when tested on the hypophysectomized rat (Leonard and Smith, 1933). Through the courtesy of Dr. Wright Clarkson of Petersburg, Va., urine from a case of teratoma testis was obtained to study the nature of this follicle-stimulating substance.*

We have applied a test to an extract of this urine that is used to differentiate hypophyseal gonadotropic hormones from those found in pregnancy urine. The test is based on the fact that there is a limitation in the

*The case history will be reported elsewhere by Dr. Clarkson.

size of the ovaries of immature female rats produced in a given period by this substance regardless of the total amount and frequency of injections. This size rarely exceeds 60 mg. (Evans, et al., 1931). With hypophyseal extracts much larger ovaries may be produced, even up to 300 mg.

Two samples of urine were employed in these experiments: the first (two morning specimens) was concentrated by the alcohol method so that 1 cc.=25 cc. of urine; the second (a 24-hour specimen and one morning specimen) was concentrated so that 1 cc.=50 cc. The first sample was injected into 14 sexually immature rats for four days with doses varying from 0.1 to 0.4 cc. and the animals were killed at the end of the fifth day. The second sample was injected into six animals at high dosages. The ages of the two groups of animals at autopsy were 30 and 28 days.

The criterion of the effective stimulation consisted in weighing the ovaries and the uteri free from fat and connective tissue. The ovaries were examined further by crushing them on glass slides and making careful examination for opaque corpora lutea, or were sectioned before examination.

The results show that with increasing doses of the extract there was an increasing response in the weight of the ovaries with doses up to 3 cc. (Table 1). Increasing the dose to 4 cc. did not cause a significant increase in weight, a response similar to that obtained with pregnancy urine. However, careful examination of the ovaries revealed in all cases only a follicle-stimulating effect, that is, the ovaries contained only large clear follicles without opaque reddish corpora lutea. The heavy uteri gave definite evidence of the follicle-stimulating effect.

The second series was injected with massive doses of extract (four animals receiving amounts equivalent to 200 cc.). The largest ovaries did not exceed those that can be produced by unlimited amounts of pregnancy urine and yet contained only clear follicles. Attempts to still further increase the dose resulted in death of the experimental animals.

It is concluded that this urine cannot produce ovaries of unlimited size in the period of treatment, and in this respect it is similar to pregnancy urine extract. On the other hand, the type of ovary produced was different from that produced by pregnancy urine, being composed solely of follicles without corpora lutea.

DISCUSSION

It is of interest that this test should apply to both of these urinary gonad-stimulating substances, yet these hormones have qualitatively different effects on the immature rat ovary. It emphasizes the fact that qualitative changes in the ovaries of the test animal should receive as much consideration as quantitative changes in studying the nature of gonadotropic hormones. Whether the follicle-stimulating substance obtained from this individual is the same as that obtained from castrated women or women past the menopause is not known, but on theoretical grounds, it would seem that they are identical.

It is known that extracts of the human hypophysis will give unlimited size ovaries in the same period of time (Leonard, 1933). It is also known that when urinary follicle-stimulating extracts and pregnancy urine extracts are injected simultaneously into young rats, large luteinized ovaries are produced (Leonard and Smith, 1933). The weights of the ovaries produced by the combined injections will exceed the limit produced by either extract alone.

Ferguson (1933) suggests that these tumors of the testes may be classified according to the amount of the gonadotropic hormone excreted. Whether the gonadotropic hormone in all classes of teratoma testis will show this distinctive character of limiting the size of the ovary is not known. Evans (1933) has been able to produce "unlimited" size ovaries with urinary extracts from an individual with a tumor of the testes but he makes no statement as to the structure of the ovaries obtained.

TABLE 1

WEIGHTS OF OVARIES AND UTERI OF IMMATURE RATS TREATED WITH URINE FROM A CASE OF TERATOMA TESTIS

Group	Treatment Urine Concentrated 25 to 1 ccm.	Autopsy Data		
		Weight of Rat grams	Weight of Ovaries mg.	Weight of Uterus mg.
1	4.	41 51	43 50	170 445*
2	3.	47 48	46 40	118 107
3	2.	43 50	29 37	110 90
4	1.	40 53	24 25	95 98
5	.5	49 48	18 24	144* 170*
6	.25	46 56	15 16	24 34
7	.10	46 59	14 13	23 32
	Urine Concentrated 50 to 1 ccm.			
8	4.	56 55	61 52	90 116
9	4.	52 45	48 57	141 127
10	2.	48 51	27 23	62 142*

*Uterus not emptied at autopsy

SUMMARY

Two samples of urine from a man having teratoma testis were tested on immature rats (14 and 6 animals, respectively). The effect was like that of pregnancy urine in that indefinite enlargement of the ovaries was not produced. It differed from that of pregnancy urine, however, in that follicular but not corpus luteum stimulation resulted.

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Abstract Department

Further studies on the tumor-inhibiting properties of adrenal extracts tested on experimental epithelioma in white mice (Nouvelles recherches sur les propriétés anti-tumorales d'extraits de surrénales vis-a-vis de l'épithelioma expérimental de la Souris blanche). Arloing, F., A. Morel, A. Josserand and A. Badinand, Compt. rend. Soc. de biol. **112:** 156. 1933.

Extracts of reticular zone from fresh calves' adrenals were made in glycerine and the proteins precipitated with perchlorid of iron. The details of the method are given. The precipitate dissolved in Locke's solution caused regression but not cure of epithelioma when injected into mice.—J. C. D.

Certain new facts about the humoral effects of exciting the sympathetic (Quelques faits nouveaux a propos du transport humoral des excitations sympathiques). Bacq, Z. M. and L. Brouha, Compt. rend. Soc. de biol. **110:** 88. 1932.

In dogs with the lower ventral roots cut and the heart and adrenals denervated, a rise in heart rate follows stimulation of the peripheral end of the sciatic, although it now contains no undegenerated motor fibers. If all preganglionic fibers to such a sciatic nerve are destroyed, the reaction is not impaired. The strength of the heart contractions, as well as their rate, is increased. These results indicate that the hormone "sympathine" is produced as the result of activity of the post-ganglionic sympathetic fibers.—J. C. D.

A note on the Viale reaction of demonstrating adrenine in body fluids (A propos de la réaction de Viale pour la mise en évidence de l'adrénaline dans les humeurs). Bacq, Z. M., Compt. rend. Soc. de biol. **110:** 564. 1932.

This reaction is the appearance of a rose color after treating the fluid with K I, $HgCl_2$, and sulfanilic acid, and boiling. This is not quantitative nor specific but reliable, if used under the conditions outlined in this paper.—J. C. D.

Secretion of sweat in horses after cutaneous injections of adrenine in serum (Secretion sudoripare chez le Cheval apres injection intradermique de serum adrenaline). Bacq, Z. M., Compt. rend. Soc. de biol. **110:** 568. 1932.

Five horses received injections in the deeper layers of the dermis of horse serum containing adrenine. Contrary to the usual results of adrenine injection in cats, adrenine stimulated sweating locally in the horse. This difference in results is explained by the fact that vasoconstrictor effects of adrenine and the small area of the paw pads obscure the reaction in cats.—J. C. D.

Effects of adrenal cortical extracts upon the blood in men (Über einige Workungen von Nebennierenrindenextrakten auf die Blutbeschaffenheit des Menschen). Bauer, J. and G. Buttu, Ztschr. f. klin. Med. **122:** 601. 1932.

The effect of cortical extracts on blood constituents, such as sugar, lactic acid, cholesterol and N.P.N., were studied on 11 patients. Changes of blood sugar were limited to small drops, ranging from 2% to 13%. They were considered to be within the range of technical errors. Changes of the N.P.N. were negligible. Determination of lactic acid, in several cases, showed inconsequential rises or drops. Injection of the extract did not produce any change in the acetone body or katalase content of the blood. The only constant and significant change observed was a drop of blood cholesterol, which was noticed 10 times in 11 cases. Blood cholesterol was determined before and three hours after injection of the cortical extracts. Some patients received 2 cc. and others as much as 10 cc. of these extracts. In two subjects the drop of cholesterol was small and did not exceed 15 points. In the remaining eight subjects the drop was substantial and ranged from 24 to 50 points. There was no relation between the amount of extract given and the extent of the drop of cholesterol. One of the cases studied was that of a girl nine years old, with precocious puberty and evidence of virilism, whose blood cholesterol was as low as 64 mg.

per cent before injection and dropped to 40 mg. per cent after administration of the cortical hormone. The authors feel that their findings corroborate previous observations according to which the cortical hormone regulates lipoid metabolism.—M. A. Goldzieher.

Cortico-adrenal hormone in urine (Investigación de la hormona cortico-suprarrenal en la orina de hombre normal y mujer embarazada). De Meio, R. H. and J. T. Lewis, Rev. Soc. argent. de biol. **9**: 113. 1933.

Urine from normal men and from women at the end of pregnancy was extracted following Swingle and Pfiffner's method for obtaining adrenal cortical hormone. The extract was injected subcutaneously to adrenalectomized rats and their sensitiveness to morphine determined. No difference was found between the treated rats and non-treated adrenalectomized controls. It is deduced that by this method it is not possible to show the elimination of adrenal cortical hormone in the urine.—J. T. L.

Studies on the adrenal; the preparation of an active extract of the hormone of the adrenal cortex. Grollman, A. and W. M. Firor, J. Biol. Chem. **100**: 429. 1933.

An active extract of the adrenal cortex was prepared from frozen beef adrenals by extracting the ground cortex with technical acetone. The epinephrine was removed by shaking a benzene extract of the active material with cold saturated Na HCO_3 solution, and the excess alkali neutralized with normal HCl. Pig adrenals were used in one preparation and were found to have three times the activity of the beef adrenals. This method yielded an extract that was colorless except in high concentrations, water clear and of low total solid content. When tested for toxicity, no effect was noticed for either mice or cats. The rat method was used for assaying the hormone. A series of four to six doubly adrenalectomized rats and varying doses comprised a test series. The rat unit was the amount of extract necessary to permit normal growth in a 40 to 50 gm. rat when given a single daily intraperitoneal injection.

—J. E. Lockwood.

A suprarenalin-producing pheochromocytoma of the suprarenal gland. Hick, F. K., Arch. Path. **15**: 665. 1933.

A pheochromocytoma was an incidental post mortem finding in a white woman of 64 dead from a rupture aneurysm of the anterior communicating artery. The tumor was adjacent to the left adrenal. The tumor was 4 by 2 by 2 cm., very soft, and deep red to dark purple-red in color. Microscopically the tumor was encapsulated and broken up into solid alveoli by fibrous bands bearing capillaries. The tumor cells were large with an abundant, finely granular cytoplasm, and round or oval nuclei with a nucleolus. Many of the cells took on a brown color after fixation in a solution of chromic acid. Suprarenalin was demonstrated in this tumor. An extract of the tumor in decinormal HCl produced a sharp, transient pressor effect in a dog. The case shows that the adrenal medulla did not require contact with the cortex to produce adrenaline. It further shows that pheochromocytoma may be present producing adrenaline and still not cause hypertension.—Author's Abst.

Circulatory aspects following experimental suprarenalectomy (Kreislaufbefunde nach experimenteller Nebenneirenentfernung). Langsdorf, O., Klin. Wchnschr. **12**: 1169. 1933.

In an attempt to produce a condition of chronic arterial hypotension 6 rabbits were doubly adrenalectomized. Femoral blood pressures were measured manometrically in 3 of the survivors which showed no complications one to four months after the removal of the second adrenal. It was found that the average resting blood pressure (79-95 mm. Hg.) was within the normal range (65-120 mm. Hg.). Clamping off both carotid sinus nerves produced a more rapid and greater rise in pressure in normal rabbits than in the operated animals, 24 mm. Hg. in contrast to 9-13 mm. Hg. Stimulation of the aortic or sinus nerves produced a similar fall in pressure in both groups but the return to normal was slower in the operated rabbits. After section of the four pressor-receptor nerves the heart rate was not increased above the initial value (202-230/min.) in the adrenalectomized series but rose to 260/min. in the normals. At autopsy the weight of the hearts of the operated group was 12% less than

that of the normals. It was concluded that the results signified a diminished sympathetic tone of the circulatory system in the doubly adrenalectomized animals.—C. tum Suden.

Effect of adrenalin upon free muscle sugar and total carbohydrate. Bischoff, F. and M. L. Long, J. Biol. Chem. **95:** 743. 1932.

A carbohydrate balance sheet for the adrenalinized fasting rat sacrificed in the recovery period. Long, M. L. and F. Bischoff, J. Biol. Chem. **98:** 85. 1932.

By a new method the tissues are plunged in boiling water for the sugar determination, frozen in CO_2 snow, shaved and hydrolyzed in 2.2% HCl for the total carbohydrate determination. Interfering substances are removed with $Zn(OH)_2$ followed by Lloyd's reagent in acid solution. Reduction values before and after fermentation with the Shaffer-Hartmann reagent give the fermentable carbohydrate. The total carbohydrate value (fermentable) does not include non-fermentable sugars, the presence of which in the filtrate were demonstrated by the Molisch and Pentose (Bial reagent) tests, the unhydrolyzed hexose phosphate which is removed by the $Zn(OH)_2$ and possibly other saccharides. In rabbit muscle (amytal anesthesia) the fermentable sugar 8 and 24 hours after the subcutaneous injection of 0.5 mg. adrenaline per kilo (10 animals) was significantly lower, 17 ± 3.3 and 17 ± 2.1 mg. per 100 gm., than that of controls (12 animals), 35 ± 1.7, 34 ± 3.3 mg. per 100 gm. In rats killed by spinal transection, the fermentable muscle sugar 3 to 4 hours after the subcutaneous injection of 0.02 mg. of adrenaline per 100 gm. was the same as that of controls. Eight hours after the subcutaneous injection of 0.10 mg. of adrenaline per 100 gm. the fermentable muscle sugar was vanishingly low in certain cases. Two interpretations of the result are given: either muscle sugar is rapidly converted to some other form in the adrenaline recovery period, or there is no post mortem liberation of glucose in the adrenalinized animal, a process taking place in normal animal tissues under the experimental conditions. The difference between total fermentable carbohydrate and glycogen was significantly greater in the control series than in the series of rabbits which had received adrenaline. This observation was interpreted as indicating that adrenaline depletes a carbohydrate reserve other than glycogen. (Later studies, however, indicate that under the conditions in which glycogen samples were taken, without control of bleeding and removal of considerable tissue, glycogen discharges took place to some extent, so that the deduction may be questioned.) Significant changes in urinary nitrogen excretion or in the fat content of the muscle were not observed during adrenaline activity. On the assumption that the peripheral tissues constitute 50% of the body weight, a carbohydrate balance sheet (for the rabbit, sacrificed under amytal anesthesia) was constructed, using total fermentable muscle carbohydrate, blood sugar, liver glycogen as determined in earlier studies, and urine sugar. For a 2 kilo rabbit, the control carbohydrate was 5543 ± 370 mg., for the adrenalinized rabbit, 3496 ± 345, indicating that 36% of the carbohydrate disappears during 8 hours' adrenalin activity (0.5 mg. per kilo). On the assumption that the peripheral tissues constitute 50% of body weight (corrected for fat content of and moisture condensation on sample in total carbohydrate determination) a carbohydrate balance was constructed (for the rat, sacrificed under spinal transection), using blood sugar, muscle total fermentable carbohydrate, muscle lactic acid, liver total fermentable carbohydrate, organ total fermentable carbohydrate and urine sugar. For a 100 gm. rat, the control carbohydrate was 286 ± 15 mgm., for the adrenalinized rat (0.02 mg. adrenaline per 100 gm.) 235 ± 16 mgm., and for the adrenalinized rat (0.1 mg. adrenaline per 100 gm.) 270 ± 14 mgm. The deficit was sufficient to account for two-thirds the calorigenic effect of the lower dose. There was no indication that fat is converted to carbohydrate during adrenal activity.—Authors' Abst.

Mechanism of pulmonary oedema following adrenine injections (Le mécanisme de l'oedème pulmonaire adrénalinique). Raposo, L. S., Compt. rend. Soc. de biol. **110:** 1038. 1932.

Injections of 0.2 to 1 mg. adrenine chloride intraventously into rabbits was followed by a rise in the blood albumin and red cell count and a fatal pulmonary oedema. The increased blood pressure caused an escape of fluid into the tissues. This finally established a balance with the increasing concentration of albumin. These untoward results can be nullified by injecting yohimbine, which has a hypotensive effect.—J. C. D.

Action of thyroxine on the secretion of adrenaline (Action de la thyroxine sur l'adrénalino-sécrétion). Zunz, E. and J. La Barre, Compt. rend. Soc. de biol. **110:** 95. 1932.

Dogs were injected intravenously with 1.5 to 3 mg. per kilo of a 1/80 N solution of synthetic thyroxine in NaOH. The adrenaline output from the adrenal vein was followed. It rose gradually after the first 20 to 45 minutes. This increased adrenine output with the consequent motilization of sugar explains why there is a hyperglycemia in these animals in spite of the fact that thyroid injections produce a very marked increase in the output of insulin. —J. C. D.

Studies on the influence of adrenine on the reduced glutathione in the blood (Recherches sur l'influence de l'adrénaline sur la teneur du sang en glutathion réduit). Zunz, E., Compt. rend. Soc. de biol. **110:** 591. 1932.

In dogs intravenous injections of adrenaline chloride of 0.22 to 0.25 milligrams per kilo body weight produced a definite increase in glutathione, reaching a maximum 4½ to 5½ hours later. Intramuscular injections gave the same result but required larger doses. This increase did not occur in decapsulated dogs.—J. C. D.

On mongolianism and other congenital degenerative conditions in their relation to advanced age of the mothers (Über den Mongolismus und andere angeborene Abartungen in ihrer Beziehung zu hohem Alter der Mütter). Bennholdt-Thomsen, C., Ztschr. f. Kinderh. **53:** 427. 1932.

A resume of the literature is given. The affected child was the first born in 20% of the cases and the last born in about 50% of the cases in the literature. There were 30 families with multiple cases of mongolianism in the 2526 cases collected by Macklin. The age of the mother (40 or above) at the time of the birth of the child may play a rôle but consanguinity has a less prominent part.—M. B. G.

Influence of endocrine system in blood disorders. Hubble, D., Lancet, **2:** 113. 1933. Abst., J. A. M. A. **101:** 1518.

The author reviews the clinical and experimental evidence relating to the effect of the thyroid, the cortex of the suprarenals, and the anterior lobe of the pituitary on hematopoiesis. It is shown that the thyroid hormone stimulates the production of red cells and lymphocytes and depresses the output of granulocytes; the suprarenal cortical hormones stimulate the production of granulocytes and possibly also of red cells, while the basophil cells of the anterior lobe of the pituitary stimulate all types of circulating cells, giving rise to a clinical picture of polycythemia. It is possible that the anterior pituitary produces this leukopoietic result indirectly through the thyroid and the suprarenal cortex. It is suggested that in hyperplasias and hypoplasias of the circulating blood cells a primary disorder of the endocrine system is the dominant etiologic factor. The clinical parallelism between exophthalmic goiter and chronic lymphatic leukemia is displayed with particular reference to Friedgood's work on the response of the basal metabolic rate, the pulse rate and the cell count in lymphatic leukemia to treatment with compound solution of iodine. It is concluded that the cause of lymphatic leukemia is a primary dysfunction of the thyroid. It is suggested that an excess of a suprarenal cortical hormone is responsible for myelogenous leukemia, and it is pointed out that polycythemia is a cardinal sign of hyperplastic conditions of the anterior lobe of the pituitary. Two hyperplasias of the bone marrow are considered, agranulocytic angina and aplastic anemia, and some further evidence is reviewed which also suggests for them an endocrine etiology.

Etiology of mongolism. Jenkins, R. L., Am. J. Dis. Child. **45:** 506. 1933.

The relation of mongolism to twinning (both members affected in monozygotic twin pairs, one member affected in dizygotic twin pairs) substantiates the belief that the immediate etiology of mongolism is to be found in the germ cell. The association of mongolism with a diminished maternal fecundity (increasing age of the mother, small size of the family and frequency of an abnormally long interval before the birth of a mongolian idiot) supports the conception that the mongolian idiot is a product of fertilization of diminished vitality of the ova.—M. B. G.

Experiments on the effect of injections of extracts from aged and embryonic animals on the growth of mice (Expériences sur l'effect des injections d'extraits et de sérum d'animaux agés et d'extraits d'embryons sur la croissance des Souris). Kaufman, L., Compt. rend. Soc. de biol. **110:** 1094. 1932.

Mice (131) were injected with extracts made by boiling 1 part of tissue with 2 of physiological salt solution. Material from young mice, from calves and cows, and from chick embryos was tested. Although such extracts accelerate the growth of tissue in culture when they are from young animals and retard it when they are from old ones, they had no influence on the growth rate of the mice. The principles acting on the tissue in culture are, therefore, not hormones.—J. C. D.

The body build factor in the basal metabolism in children. Lucas, W. P. and H. B. Pryor, Am. J. Dis. Child. **46:** 941. 1933.

Children of slender build (linear type) normally have higher basal metabolic rates than broadly-built children of the same age-sex group. Differences in oxygen requirement are not determined by nutritional variations in children. The slenderly built children use more oxygen per unit of weight and per unit of body surface than broadly built children of the same age-sex group. Surface area measurements apparently show up the same differences in persons that the width-length index of body build does.—M. B. G.

Mongolism in monozygotic twins. Lund, S. E. T., Am. J. Dis. Child. **46:** 811. 1933.

The number of recorded cases of mongolism in one of presumably dizygotic twins is 38 and of monozygotic twins (both being mongolian idiots), 7 with the present case. There are six additional cases which do not permit classification. This makes a total of 51 cases of mongolism in twins. In this report, the twins were the eleventh of 12 births resulting in 14 children. The father was 51 and the mother 44 years of age at the time of birth of the patients. A diagnosis of monozygotic condition was made on the method of Stocks and on the basis of anthropometric measurements and fingerprints.—M. B. G.

Interpretation of basal metabolism in children. Talbot, F. B., J. Pediat. **3:** 247. 1933.

Metabolic data from thin and fat children must be interpreted with care and cannot be compared with any standard in which total heat production is divided by the weight alone or as part of some formula (e.g., with tables of the average number of calories per kilogram of body weight or of the total number of calories per square meter of body surface. The surface area of the body is estimated from a formula which includes weight). Measurements obtained from tall and short children of normal weight are comparable with standards of calories per square meter, calories per kilogram and total calories for height and weight. Figures from underweight children are comparable with total calories for height, total calories for expected weight, calories per kilogram of expected weight and calories per square meter of body surface if the expected weight is used in the formula for body surface. It is technically easy to determine the metabolic level; often difficult to establish and maintain basal conditions especially in children under 8 years of age and always very difficult to interpret intelligently the figures obtained wthout any knowledge of all the technical and physiological factors which affect the significance of the standards.—M. B. G.

Lowered basal metabolism in conditions characterized by slow pulse rate. Schick, B. and A. Topper, Am. J. Dis. Child. **45:** 760. 1933.

Schick and co-workers postulated the theory that "the lowered post-infectious metabolism is caused by more or less generalized cellular damage which at times hits the endocrine glands especially, rather than by stimulation of the vagus." This is confirmed by the present paper which reports the result in studies of basal metabolism of 52 cases of bradycardia occurring in various conditions; postfebrile stage of acute infections, in recent hepatic disease with icterus, in cerebral tumor and in epilepsy and chorea.—M. B. G.

Standards of basal metabolism for children of retarded growth. Topper, A., Am. J. Dis. Child. **45:** 1209. 1933.

The five standards of basal metabolism are total calories referred to height, to sitting height, to weight, to surface area and to age, and seem to bear a fairly constant relationship to the total metabolism of normal children. These may be used with safety in the obese child and thin child but not in the child with retardation of growth. The report is based on studies on the basal metabolism of 20 children who were greatly retarded in growth but normal in all other respects. The figures obtained do not conform to any of the standards usually used, except the total calories referred to age. The greater the disproportion between the actual stature and the expected stature for the age, the greater the discrepancy between observed basal metabolism and expected basal metabolism by all standards except total calories regerred to age. It is suggested that the reason underdeveloped children conform to this standard is that while their physical proportions have remained underdeveloped, the growth of the inner organs, and therefore the actual cellular activity of the body, has proceeded normally, commensurate with their age, the age being a truer measure of actual cellular activity and therefore of heat production than such body measurements as height, sitting height, surface area or weight. In evaluating figures obtained from tests on the basal metabolism made on children who were much retarded in growth, each child should be considered as a standard for himself; changes in the metabolic rate that may occur from time to time should be referred to the individual basal rate of that particular child rather than to any known standards of metabolism, except perhaps that referred to age, as all other standards are too low for this type of child.—M. B. G.

The ovaries and testes of foetal horses as a source for hormones (Les ovaires et les testicules des foetus de cheval comme source d'hormones). Brill, J., Compt. rend. Soc. de biol. **113:** 951. 1933.

In 15 embryos it was noted that the gonads were large. Analyses indicated a high folliculin content. These organs are probably the source of the large amounts of folliculin found in pregnant mares.—J. C. D.

The inhibitory action of folliculin on deciduomata in rabbits (Action empêchante de la folliculine sur le déciduome, chez la lapine). Brouha, A., Compt. rend. Soc. de biol. **110:** 1023. 1933.

In 14 rabbits threads were implanted in the uterus at varying periods after mating. False pregnancy, as indicated by decidual changes, invariably followed when the implantation was made on the 6th day. Folliculin, 100 to 300 rat units, was given 8 animals after mating. The implantations in these failed to give any reaction. The effect of corpus luteum on the uterus was, therefore, antagonized by folliculin.—J. C. D.

Note on experimental cryptorchidism in guinea pigs (A propos de la cryptorchidie expérimentale chez le cobaye). Brouha, L. and L. Desclin, Compt. rend. Soc. de biol. **112:** 214. 1933.

In all animals examined (number not given) three months after fixation of the testicle within the abdomen, there were a large number of tubules showing active spermatogenesis.—J. C. D.

Passage of hormones from mother to foetus (Ricerche sperimentali sul passaggio degli ormoni dalla madre al feto attraverso la placenta). Cattaneo, L., Arch. di fisiol. **32:** 133. 1933. Abst., Physiol. Absts. **18:** 518.

Gravid ewes between half and full term were prepared in such a way as to allow simultaneous registration of the arterial pressures of the mother and foetus, and various substances were then injected into the jugular vein of the mother. After the injection of 1 to 5 cc. of 1% adrenaline there was a marked increase in the amplitude of the foetal heart beats and a rise in its blood pressure, these changes beginning rather later and enduring much longer than the corresponding changes in the maternal circulation. In one case injections of adrenaline were made both before and after section of both vagi of the foetus, and the effect was much greater in the second case. Injection into the mother of 1 cc. of acetylcholine (strength not stated) was followed by very rapid fall in

blood pressure and death of the foetus, although the mother survived; death of the foetus could be prevented by subsequent injection of adrenaline into the mother. After the injection of 2 cc. of pituitrin into the mother there were rises in the blood pressures of both individuals, these taking place before the onset of contractions of the uterus.

Hormonal sterilization of female organism. Mandelshtam, A. E., and V. K. Chaykoviskiy, Vrach. delo, **15:** 99. 1932. Abst., J. A. M. A. **100:** 1734.

The authors proved in a previous study that injections of prolan B in animals cause a temporary sterility. The resulting formation of corpora lutea arrests follicular growth, creating a state of pseudopregnancy. The authors made observations in ten women with normal menstrual cycle about to be operated on for some such condition as uterine fibromyoma, cancer of the cervix or cyst of one ovary. Freshly prepared prolan was administered in doses of from 100 to 200 mouse units until, in the course of a few days, the patients received from 400 to 1,100 mouse units. They were operated on from two to twenty-six days after the last injection. Serial histologic sections of ovarian tissue removed at operation demonstrated in each case defective ova in the maturing and matured follicles, disintegration and disappearance of the membrana granulosa, cystic dilatation of the follicles, development of numerous corpora lutea, and hyperemia and hemorrhages into the follicular tissue. The degenerative changes produced render the follicles insusceptible of being fertilized. The authors concluded that (1) various doses of prolan are well borne by women; (2) administration in the course of a few days of from 400 to 1,100 mouse units of prolan results in profound degenerative changes in the follicular apparatus; (3) the histologic changes produced suggest that the foregoing doses are sufficient to cause sterility. They question the harmlessness of temporary hormonal sterilization for the general health of the organism as well as for future generations. The absence of degenerative changes in the ovaries of pregnant women is to be explained by the protecting antagonistic action of other hormones present.

The oestrous-stimulating power of powder from follicular liquid 22 years after drying (Activité oestrogène d'une poudre de liquide folliculaire 22 ans apres sa dessiccation). Choay, A. and S. Faure, Compt. rend. Soc. de biol. **110:** 936. 1932.

The follicular liquid was dried over sulphuric acid in vacuo and stored in glass bottles, closed with cork or ground glass stoppers, and protected from light. Material from mares and cows lost none of its original potency after 2 to 4 years. A sample from sows, 22 years old, produced the typical oestrous changes in spayed rats.—J. C. D.

Production of estrus; relationship between active principles of placenta and pregnancy blood and urine and those of the anterior pituitary. Collip, J. B., H. Selye, Evelyn M. Anderson and D. L. Thompson, J. A. M. A. **101:** 1553. 1933. Abst., A. M. A.

The authors state that the anterior pituitary-like gonad-stimulating substance of the human placenta and of human pregnancy blood and urine causes merely thecal luteinization when administered to hypophysectomized immature rats, to very young suckling rats or to guinea-pigs. Hence, when in the normal rat it produces enlargement of follicles and formation of corpora lutea, it does so by virtue of the presence of a complementary substance produced by the pituitary of the test animal. The authors demonstrated the presence of this complementary substance in pituitary extracts and suggest that it may be identical with the substance which enhances the action of the anterior-pituitary-like hormone on the ovaries of normal rats.

Biological difference in response of the female macacus monkey to extracts of the anterior pituitary and of human pregnancy urine. Engle, E. T., Am. J. Physiol. **106:** 145. 1933.

This paper represents a preliminary statement on the reaction of the ovaries of macacus monkeys which have been studied during a three-year period. Ovaries of 37 animals from various series of experiments have been studied. The animals ranged in weight from 1800 grams to 5150 grams. Ex-

tracts of the anterior pituitary gland cause follicular growth and cystic development in the monkey ovary. Six to ten days after initiation of treatment in sub-adult animals and usually in immature monkeys, ovarian activation is evidenced by changes in the sex skin; reddening, turgosity, pachydermatous foldings. Adult animals show a lesser degree of external response. Slight theca lutein changes are produced by this treatment with subcutaneous injections, but no typical lutein bodies have been formed by this method. When using the gonad-stimulating substance from pregnancy urine no such response has been obtained in immature, subadult or mature female monkeys. Since no activation of the sex skin has occurred with subcutaneous or intravenous injections for as long as 32 days, it is concluded that, as used, there is no follicular activation. Instead of follicular growth there appears to be a cessation of ovarian activity, with atresia of large follicles and hyalinization of the small follicles. It is emphasized that this substance derived from human pregnancy urine is not known to be present in macacus monkeys during any physiological state, and, as used, is a depressant rather than a stimulant of follicular development in the monkey ovary.—Author's Summary.

Sex antagonism and spontaneous feminization in male guinea pigs carrying ovarian grafts (Antagonisme sexuel et féminisation spontanée de cobayes males entiers par greffe d'ovaires). Guyénot, E., W. Bartschi and K. Ponse, Compt. rend. Soc. de biol. **110:** 895. 1932.

Of 17 male guinea pigs, carrying ovarian grafts in the kidney but otherwise normal, 4 developed female characters. Of 36, castrated at the time the ovarian tissue was implanted, 16 showed similar changes.—J. C. D.

Human ovarian responses to extracts of pregnancy urine—preliminary report. Hamblen, E. C., Virginia M. Monthly, **60:** 286. 1933.

Ovarian responses to Antuitrin-S in 11 women and girls are reported. Subjects presenting evidence of pelvic inflammation and, in general, older subjects were excluded. The total dosage ranged from 1200 to 8000 r.u. given subcutaneously. No luteal stimulation and no "hemorrhagic responses" were observed. The response in immature and adolescent ovaries was not more marked than in the adult. Follicle activation apparently occurred, terminating in atretic degeneration and corpora candida formation.—R. G. H.

On the mechanism of action of the follicular hormone (Zum Wirkungsmechanismus des Sexual (Follikel) Hormones; zur Frage der hormonalen). Haupstein, P., Endokrinologie, **10:** 321. 1932.

The ovaries of normal mice, following daily injections of small doses of ovarian follicular hormone (1 to 5 m.u.) during a period of 14 days, showed a normal maturation cycle. Doses of 50 to 100 m.u. in normal mice prevented the formation of follicles and corpora lutea. Haupstein considered the possibility of sterility succeeding such gonadal impairment. Therefore, a series of 5 fully mature mice and a second group of 5 mice in early maturity were injected daily with 100 m.u. of ovarian follicular hormone for 14 days, given an 8-day rest interval and then mated. Four of the 5 in the first series were sterile, and the fifth had a litter of 8. The second series showed 3 sterile and the remaining 2 had litters of 6 each. A control series of 10 mice showed 4 sterile and the remainder had litters totaling 30. Metestrus was observed in the test group of mice 5 days after the injections were discontinued, hence the author concludes that the induced state of infertility is transitory.—E. A. Sharp.

Differential effect of prolan in decreasing the potency of the hypophysis in normal and castrate rats. Leonard, S. L., Anat. Rec. **57:** 45. 1933.

Normal male and female rats were injected for 10 days or longer with pregnancy urine extract (prolan), i.e., 10 R.U. daily. The anterior pituitaries of these animals were implanted into immature female mice, the littermates of which received pituitaries from uninjected males and females as control. The average weight of the ovaries of the mice which received implants from the injected male donors was 42.4% less than the weight of the ovaries from control donors. In the females, the average ovarian weight was 33.7% less. If the donor males or females were first castrated, the injection of prolan was without effect on the gonad-stimulating power of the pituitary when tested in

a similar manner. It is concluded that the pregnancy urine extract induces an overproduction of the respective sex hormone in the normal injected animals which in turn depletes the hypophysis. In the absence of the gonads, this does not occur. Consequently, prolan has apparently no direct physiological effect on the pituitary.—Author's Abst.

Effects of different anterior pituitaries and human pregnancy urine on rat sex organs. Loeb, L., Proc. Soc. Exper. Biol. & Med. **30**: 1330. 1933.

In former investigations it was found that anterior pituitaries of different species as well as urine of pregnancy have each a specific action on the sex organs of the guinea pig. The anterior pituitaries of rat, rabbit, cat and guinea pig caused enlargement and maturation of follicles, formation of pseudo-corpora lutea, interstitial gland and in some cases ovulation, but there are quantitative differences between the effects of the glands of these different species. The pituitary substance of cattle, hog and sheep produce an intense atresia of follicles and give rise to the formation of small pseudo-corpora lutea and of interstitial gland which are caused by the hypertrophy of the theca interna and connective tissue elements. Urine resembles in certain respects the anterior pituitaries of rabbit and rat but differs in that it does not produce large mature follicles in the ovaries. In the present investigation the effects of these various substances on the guinea pig were compared with those on the rat. In certain essential respects these different preparations of anterior pituitaries and of urine of pregnancy have a similar effect in the rat and in the guinea pig, but there are also some differences. In the rat, urine of pregnancy behaves in a similar way to anterior pituitary of the rat and rabbit. The follicles mature and then the blood vessels grow into the granulosa which becomes converted into lutein tissue so that pseudo-corpora lutea develop which inclose the ova. In some follicles the intrafollicular fluid increases in amount and dilates the follicular cavities. The vagina undergoes keratinization, the uterine epithelium increases in size; the mammary gland proliferates. Just as in the case of the guinea pig, so also in the rat, the guinea pig anterior pituitary is very much less effective than the glands of the other species, but in principle the effects are similar. Extracts of anterior pituitaries of cattle do not cause the marked maturation of follicles as do the anterior pituitaries of the other species. The follicles grow only to a limited extent and subsequently pseudo-corpora lutea form which represent hypertrophic atretic follicles in which as a rule the granulosa has been previously destroyed. The vagina is relatively inactive; the uterus and mammary gland proliferate slightly or not at all. Therefore, the effect of cattle anterior pituitary on the sex organs of the rat resembles the action on the sex organs of the guinea pig, but in the latter the degeneration of the granulosa and atresia of follicles are very prominent and they are absent in the rat. This difference is presumably due to a greater power of resistance to injurious influences possessed by granulosa cells of the rat follicles as compared with those in the guinea pig ovary. This increase in resistance in the rat is also indicated by lack of degeneration of these granulosa cells at the time of ovulation. This characteristic feature enables the rat to have such a short sexual cycle and it explains the ovulation of so many follicles at the beginning of the cycle in the rat.—H. Friedman.

New test for diagnosis of pregnancy; hormonal hypercholesterolemia (Une nouvelle épreuve biochimique pour le diagnostic de la grossesse, l'hypercholestérolémie hormonale). Masciottra, R. L. and R. Martinez de Hoz, Presse méd. **41**: 293. 1933. Abst., J. A. M. A. **101**: 90.

Masciottra and Martinez de Hoz present a preliminary report on a biochemical method based on the facts that prehypophyseal hormone increases cholesterolemia and that the urine of pregnant women contains the prehypophyseal hormone. It was found in a series of experiments that the injection of urine of pregnant women into guinea pigs of either sex produced, within the first twenty-four hours an increase of cholesterol in the blood amounting to from 30 to 50%. The reaction was positive at various stages of pregnancy. In a control series of experiments it was found that the urine of non-pregnant women (surgical control) did not produce the increase of cholesterol observed in the other experiments. Slight variations of less than 5% were observed in a few instances, which may have been due to error in colorimetric readings. The method used in these experiments was as follows: Ten cubic centimeters

of urine obtained from the fasting patient by catheterization was mixed with 25 cc. of sulphuric ether. After the mixture had been shaken and decanted, 10 cc. was injected into a guinea pig. After twenty-four hours, blood was withdrawn from the heart of the animal with a syringe containing crystallized potassium oxalate, and its cholesterol content was determined by the method of Grigaut. This test of hormone hypercholesterolemia is considered positive by the authors if the blood cholesterol of the guinea pig is increased 25%. They think the test has several advantages over the Aschheim-Zondek reaction. The test animal is easier to procure, as it may be male or female, sexually mature or immature and of any age or weight. The withdrawal of blood does not necessitate killing the test animal. The technic is simple and the test can be performed in twenty-four hours.

The influence of the uterus on the secretion of folliculin by the ovary (L'influence de l'utérus sur la sécrétion folliculaire de l'ovaire). Mavromati, L., Compt. rend. Soc. de biol. **110:** 651. 1932.

In five rats hysterectomy was followed by prolonged oestrous. In three rats, with prolonged oestrous, autopsy showed atrophied uteri. These results indicate either that the uterus destroys large amounts of folliculin or that it inhibits its formation by the follicle. When the uterine influence is withdrawn, there is an excess of folliculin which acts on the vaginal mucosa to produce the typical picture of active oestrous.—J. C. D.

Studies on the gaseous metabolism of rabbits following injections of the gonadotrophic principle of the urine of pregnant women (Recherches sur le métabolisme gazeux du Lapin après injection du principe gonadotrope de l'urine de Femme enceinte). Mayer, A., Compt. rend. Soc. de biol. **110:** 237. 1932.

Rabbits of both sexes were injected with 20 to 30 mouse units per day of urine extract. This was sufficient to produce the Aschheim-Zondek reaction. Carefully controlled observations failed to show any change in the rate of gaseous exchange as compared with normal animals.—J. C. D.

Ovarian insufficiency and mental disorders. Nerancy, J. T., D. L. Steinberg and J. H. Hutton, Clin. Med. & Surg. **40:** 586. 1933.

This article deals with 17 cases of primary ovarian insufficiency found among 175 cases of endocrine dyscrasia occurring among patients at the Elgin (Ill.) State Hospital. The diagnosis was based on (1) the menstrual history, (2) exclusion of non-endocrine causes of the menstrual disorders, (3) exclusion of other endocrine dyscrasias, and (4) inclusion of positive findings of ovarian insufficiency—long lower measurement, lowered glucose or galactose tolerance, lymphocytosis, gastro-intestinal upsets, abdominal pain, nausea and vomiting. Treatment consisted of the administration of theelin, ovarian residue, corpus luteum and progynon. Of the 17 patients 9 have been discharged and 1 paroled. Some improvement has occurred in others but has not proceeded to the stage where they can be discharged or paroled. Consequently no improvement is recorded. There were 12 cases of dementia praecox, 4 of the paranoid type (1 discharged); 4 hebephrenic (1 discharged and 1 paroled); 2 catatonic (both discharged); and 2 unclassified (1 discharged). A table is included showing the mental diagnosis, treatment administered and the outcome.—J. H. Hutton.

Ovarian tumors associated with secondary sex changes; granulosa cell carcinoma and arrhenoblastoma. Novak, E. and J. H. Long, J. A. M. A. **101:** 1057. 1933. Abst., A. M. A.

The authors give their conclusions based on the study of material from 26 cases of granulosa cell ovarian tumors and two cases of arrhenoblastoma, together with a number of other cases of other tumors of this embryonic class, particularly disgerminoma (seminoma) and the so-called Brenner tumor (oophoroma folliculare). The especial points that they stress are (1) the feminizing tendency of the granulosa cell group, dependent on the production of folliculin by the constituent cells, and (2) the defeminizing and masculinizing tendencies of the arrhenoblastomas. The latter capacity is believed to be due to the origin of the tumors from certain undifferentiated cells in the region of the rete ovarii, which is the female homologue of the testis. The intersexual

phenomena that may be brought about by these rare tumors are of great biologic interest, especially as they are not unlike the phenomena that may be observed with certain lesions of the suprarenal cortex. The authors report an additional case of arrhenoblastoma and discuss briefly the factors concerned in sex differentiation, for without some knowledge of this still somewhat nebulous subject the pathologic physiology of these tumors cannot be intelligently studied.

Observations on the descent of the testes in the macaque and in the chimpanzee. Wislocki, G. B., Anat. Rec. **57:** 133. 1933.

The male macaque monkey exhibits at birth swelling and turgescence of the scrotum accompanied, as a rule, by the presence of descended testes. Shortly after birth the testes undergo ascensus into the inguinal canal while the scrotum regresses until it becomes a flattened fold of skin between the thighs. Not until the course of the third to fifth year do the testes descend again permanently, at which time the scrotum again becomes fully formed. In the chimpanzee the testes descend permanently into the scrotum before birth. Well-defined scrotal anlagen are present in the macaque and chimpanzee before birth, and throughout adult life the scrotum is well developed in normal, healthy animals. The turgescence of the scrotum in the macaque at birth and its subsequent regression accompanied by ascent of the testes can plausibly be attributed to hormonal factors. The phenomena in the male macaque at this period bear a resemblance to changes described in the human around birth. They also resemble very strikingly effects produced by Engle in young monkeys by administration of extracts of pregnancy urine or of anterior lobe.
—Author's Abst.

Variation in susceptibility of the thyroid in mammals of different species to the thyroid-stimulating substance of the anterior lobe of the hypophysis and of the ovary to gonadotropic hormone (Differences de sensibilité selon l'espèce, chez les mammifères, de la thyroïde a la thyréo-stimuline préhypophysaire et de l'ovaire a la gonado-stimuline). Aron, M., Compt. rend. Soc. de biol. **110:** 716. 1932.

The thyroid of guinea pigs responds most easily. Rabbits respond less easily and rats and mice require a dosage 150 to 200 times as great as that given guinea pigs before their thyroids show the same changes. A similar relation exists in the response of these forms to the ovarian-stimulating substance derived from the hypophysis, placenta, or urine of pregnancy.—J. C. D.

The onset of acromegaly before 15 years of age. Atkinson, R. F. B., Brit. J. Child. Dis. **28:** 121. 1931.

A description of cases in the literature on this subject is given. The author mentions 32 cases but rejects 7 as not being authentic.—M. B. G.

Extract of anterior lobe of the hypophysis and resistance to insulin (Extrait antéro-hypophysaire et résistance a l'insuline). di Benedetto, E., Compt. rend. Soc. de biol. **112:** 499. 1933.

Normal dogs (9), 2 without hypophyses and 2 without thyroids, were injected with anterior lobe extract for 5 or 6 days. At the end of this period they were much more resistant to the action of insulin as shown by its depressing and fatal effects than were untreated controls.—J. C. D.

Pituitary and nitrogen metabolism in toads (Hipófisis y metabolismo nitrogenado en el sapo). Braier, B., Rev. Soc. argent. de biol. **9:** 72. 1933.

Hypophysectomized toads (Bufo arenarum) eliminated 30% less nitrogen in urine than craneotomized controls. Implantation of anterior pituitary lobe did not modify the urinary nitrogen in normal and craneotomized controls. It increased the urinary nitrogen in hypophysectomized toads to normal figures. Pancreatectomy increased urinary nitrogen 31% in respect to the amount eliminated by the same animal before operation. Toads without pancreas and pituitary had a normal nitrogen excretion. Implantation of anterior lobe in these animals produced an increase in urinary nitrogen to a level seen in the pancreatectomized animals.—J. T. L.

Transmission by the blood stream of the polyuria and hypochloruria following hypophysectomy (Transmission par voie sanguine de la polyurie et de l'hypochlorurie hypophysaires). Brull, L., Compt. rend. Soc. de biol. **110:** 92. 1932.

The kidney circulation of one dog was anastomosed with the circulation of two other dogs, one normal and one hypophysectomized, and used as an indicator. Perfusion with blood from the hypophysectomized animal produced the characteristic polyuria and hypochloruria. Twenty-four animals were used in eight experiments.—J. C. D.

Cyclic histological variations in the anterior hypophysis of the sow (Sus scrofa). Cleveland, R. and J. M. Wolfe, Am. J. Anat. **53:** 191. 1933.

There are cyclic histological changes in the anterior hypophysis of the domestic sow, which can be correlated with the cyclic changes of the ovaries and the accessory organs. The cyclic changes in the hypophysis are both quantitative and qualitative; the qualitative changes predominate. During prooestrus, the relative percentage of the cells of type III (basophiles) which contain granules material is high. During oestrus, few of these cells contain granules. During the early lutein phase there is a high percentage of the cells of type III which contain granules. However, granules are not observed in these cells during the middle and latter parts of the lutein phase. During oestrus, the cells of type I (eosinophiles) are packed with granules which stain intensely with orange G. During the lutein phase these cells contain a small amount of granular material which stains lightly with orange G. The cells of types I and II apparently lose their granular material and give rise to the cells of type IV (chromophobes). The relative percentage of the cells of type IV is greatest at the end of the lutein phase. Cell counts were made on all sections studied.—Authors' Abst.

The anterior lobe of the pituitary and the reaction of the melanophores (Le lobe antérieur de la glande pituitaire et la réaction des mélanophores). Collin, R. and P. L. Drouet, Compt. rend. Soc. de biol. **110:** 1151. 1932.

The anterior lobe of guinea pigs and of beef produced a very definite expansion of the melanophores when transplanted into frogs. The degree of the reaction varies but it is not due to contamination with pars intermedia.

—J. C. D.

Extracts of the posterior hypophyseal lobe and changes in weight in the frog Extrait post-hypophysaire et variations pondérales chez la grenouille). Collin, R. and P. L. Drouet, Compt. rend. Soc. de biol. **110:** 1153. 1932.

Five frogs after injection with posterior lobe extract showed the typical expansion of the melanophores. They did not, however, show the expected oedema and their weights varied no more widely from day to day than those of controls.—J. C. D.

Blood sugar studies following hypophysectomy and experimental lesions of hypothalamus. D'Amour, M. C. and A. D. Keller, Proc. Soc. Exper. Biol. & Med. **30:** 1175. 1933.

Low blood sugars occurred in 8 of 12 hypophysectomized dogs and in 5 of 13 dogs with transverse chiasmal lesions, but not in dogs with other types of hypothalamic lesions. Glucose tolerance curves were high in all following operation but returned to normal. After starvation, tolerance curves were higher and more prolonged in the hypophysectomized and chiasmal dogs than in normal.—M. C. D'Amour.

Action of alkaline extracts of anterior lobe on immature female guinea pigs (Action des extraits préhypophysaires alcalins sur la femelle immature du cobaye). Guyenot, E., A. Fehr and A. Moszkowska, Compt. rend. Soc. de biol. **110:** 19. 1932.

It has been claimed that guinea pigs do not respond to injections of extracts of anterior lobe of the hypophysis. If large doses of alkaline extract are injected, however, marked changes are produced in the ovaries characterized by degeneration of the egg and granulosa, and hypertrophy of the theca interna. The vagina remains infantile. The thyroid becomes overactive.—J. C. D.

Anterior pituitary extract and hyperglycemia produced by morphine and adrenaline (Extracto antero-hipofisario e hiperglucemias adrenalínica y morfínica). Houssay, B. A. and E. di Benedetto, Rev. Soc. argent. de biol. **9:** 78. 1933.

Normal dogs on meat diet received 5 daily injections of Evans and Simpson's bovine anterior lobe extract (7 cc. per kg. daily, 1 cc.=0.2 gm. fresh anterior lobe). After 18 hours' fast 0.25 mg. epinephrin per kg. was injected. The blood sugar curve was followed during 9 hours. The initial level was higher and the increase after epinephrine was greater in the treated animals than in normal controls. The experiment was repeated with morphin and a more pronounced hyperglycemia was also seen.—J. T. L.

Hypophysis and thyroid; action of anterior lobe extracts on the weight of the thyroid (Hypophyse et thyroïde. Action de l'extrait du lobe antérieur de l'hypophyse sur le poids de la thyroïde). Houssay, B. A., A. Biasotti and P. Mazzocco.

Hypophysis and thyroid; action of anterior lobe extracts on the histology of the dog's thyroid (Hypophyse et thyroïde. Action de l'extrait anté-hypophysaire sur l'histologie de la thyroïde du Chien). Houssay, B. A., A. Biasotti and A. Magdalena, Compt. rend. Soc. de biol. **110:** 832; 834. 1932.

Following intraperitoneal injections of anterior lobe extract into dogs, there was an initial drop in thyroid weight followed by a marked increase over that of controls. This held for young and adult animals, unoperated animals, and those deprived of one lobe of the thyroid or of the entire hypophysis. Histologically there was a picture of increased activity with resorption of colloid and parenchymal hyperplasia. This picture was seen also in thyroid grafts in treated animals. The effect of the hypophyseal extract was nullified when thyroid extract was given at the same time.—J. C. D.

Is the thyroid-stimulating hormone of the anterior lobe of the hypophysis eliminated by the kidney (L'hormone thyréostimulante préhypophysaire est-elle éliminée par le rein)? Krogh, M. and H. Okkels, Compt. rend. Soc. de biol. **113:** 638. 1933.

Thirteen guinea pigs were injected with extracts of urine (A) from hyperthyroid cases, (B) from 5 guinea pigs receiving injections of anterior lobe, (C) from a normal subject, (D) from the same normal urine to which "thyrostimulin" had been added before extraction began. The animals receiving the artificially hormonized urine showed the characteristic thyroid changes. The other animals did not. The thyrostimulin is, therefore, not found in the urine of hyperthyroid cases and appears not to pass through the kidneys of guinea pigs.—J. C. D.

A specific sex difference in the anterior lobe of the hypophysis in the rat (Différences préhypophysaires spécifiques du sexe chez le rat). Lipschütz, A. and G. Reyes, Compt. rend. Soc. de biol. **109:** 1330. 1932.

Twelve grams of extract of male rat hypophysis was given young female rats. Follicular development and luteinization resulted. Equal amounts of extract from female rat hypophysis were ineffective but three times the dose produced follicular development without luteinization. The female hypophysis, as compared with the male, is deficient in both prolan A and prolan B.—J. C. D.

The preparation of thyreotropic extracts of the anterior lobe (Die Darstellung thyreotrop wirksamer extrakte aus Hypophysenvorderlappen). Loeser, A., Arch. f. exper. Path. u. Pharmakol. **166:** 693. 1932.

A method, depending upon acetone precipitation, for the preparation of active thyreotropic extracts of the anterior hypophysis is described. As an assay method the thyroids of immature guinea pigs which had been injected with the extract for three days were studied for indications of stimulation. No statement is made regarding the number of animals employed in these studies. The active principle is not soluble in the ordinary organic solvents, but is soluble in aqueous alcohol, acetone, or pyridine as well as water and dilute acids and alkalies. In aqueous solution it gives a positive biuret reaction. Aqueous solutions rapidly lose their activity, but this may be prevented by the addition of

5% phenol. The dry powder may be stored without loss of activity. The active principle is destroyed when heated at 100 degrees C. Reaction of the active substance toward benzoyl chloride, diazotization, as well as toward various precipitants is described.—W. O. Nelson.

Cellular development and secretory phenomena in the anterior lobe of the hypophysis studied by the silver impregnation method (La cytogenèse et les phénomènes sécrétoires du lobe antérieur de l'hypophyse étudiés par la méthode de l'imprégnation argentique).

Further results of the application of silver staining to the study of the hypophysis (Nouveaux résultats de l'application de l'imprégnation argentique a l'étude de l'hypophyse). Morato, J. X., Compt. rend. Soc. de biol. **110:** 1028; 1029. 1932.

In the cat, the cytoplasm of the resting cell of the anterior lobe is clear and stains a yellowish gold. Under activity it becomes first brownish, and then shows more and more granules which stain with silver. These black staining granules gradually change to a non-staining substance, so that the cell then appears vesicular. These cells are described in detail and the occurrence in the intermedia noted. In embryos, the resting form predominates.—J. C. D.

Posterior hypophyseal extract and imbibition in Batracians (Extrait postérohypophysaire et imbibition des Batraciens). Novelli, A., Compt. rend. Soc. de biol. **112:** 506. 1933.

Toads and frogs were kept in water up to the edges of their mouths for 24 hours before and after receiving varying doses of posterior lobe extract. Under these conditions there is a rise in water absorption. With a dose of 5 milligrams of powdered extract per 100 grams, there was a 16% to 17% increase in weight, maximum at 10-12 hours after injection. A graph showing results given by 140 toads is included.—J. C. D.

Hypophysectomy in the pregnant rat. Pencharz, R. L. and J. A. Long, Am. J. Anat. **53:** 117. 1933.

The hypophysis was removed in rats pregnant 4 to 21 days; incompletely in 26 cases, completely in 67. Of the 26, 22 gave birth to normal young; 4 showed marked disturbances in the birth mechanism. The 67 complete hypophysectomies include 28 rats operated on on the fourth to the tenth day of pregnancy, 39 rats on the eleventh to the twenty-first day, inclusive. Animals operated on on the fourth day of pregnancy fail to implant; hypophysectomy on the seventh to the tenth day of pregnancy is followed by resorption. Mothers operated on between the eleventh and twentieth days die or give birth to living young at the end of prolonged gestation; while after removal on the twenty-first day normal parturition occurs at term. The eleventh day is the critical point between resorption and continued pregnancy. The corpora lutea of pregnancy in normal rats and those in rats hypophysectomized on the twelfth day or later are indistinguishable. Normal parturition occurs in the absence of the posterior lobe and with only fragments of the anterior lobe present. Mammary development continues in the absence of the hypophysis, but in no case is milk secreted.—Authors' Abst.

Phosphocreatine and glutathione in muscle of hypophysectomized toads (El contenido de fosfocreatina y de glutatione del músculo de los sapos hipofisoprivos). Marenzi, A. D., Rev. Soc. argent. de biol. **9:** 43. 1933.

The anterior pituitary lobe was extirpated in toads (Bufo arenarum). Phosphocreatine was determined by Fiske and Subbarow's method after taking the following precautions: the sciatic nerve was cut so as to ensure immobility of the gastrocnemius used; the animal was put in the ice box at 2-3° C., one hour before taking the sample; all operations were performed at low temperature. A 33% decrease in phosphocreatine and a 30% decrease in total phosphorus was seen when asthenia was at its height, compared with results obtained in normal controls. A decrease was also found in the glutathione content of muscle and liver 40 days after operation. Implantation of anterior lobe and injection of bovine anterior pituitary extract abolish asthenia and increase the phosphorus, phosphocreatine and glutathione content to almost normal figures.—J. T. L.

Cyclical phenomena produced in rats by section of the pituitary stalk and their possible relation to pseudo-pregnancy. Richter, C. P., Am. J. Physiol. **106:** 80. 1933.

Five rats in which the pituitary stalk had been sectioned showed extraordinary cycles in spontaneous activity and food- and water-intake. The infrequency of the activity cycles was characteristic for each animal, 9.6, 11.2, 13.0, 14.3, and 18.4 days. The group average was 14.0 days. The cycles were characterized by sudden bursts of activity at regular intervals with a relatively low plateau between. Food- and water-intake were the lowest when the activity rise occurred, and highest midway between. This phenomenon appeared only in females. Vaginal smears showed cornified cells on the day the burst of activity occurred and dioestrous smears on the intervening days. Ovariectomy completely eliminated all the cycles in activity and food- and water-intake as well. In an attempt to assign the origin and significance to these cycles, it was pointed out that they probably represent even multiples of the fundamental 4 to 5 ovulation cycles. The possible relation between the activity cycles produced by section of the pituitary stalk and the phenomenon of pseudo-pregnancy is also probably timed as a multiple of the 4 to 5 cycle. It was concluded that the cycles originated in the ovaries rather than in the pituitary gland, otherwise the 4 to 5 day cycles would be found in the male as well.

—Author's Summary.

Anatomical connections between the hypothalamus and the hypophysis (Rapports anatomiques de l'hypothalamus et de l'hypophyse). Roussy, G. and M. Mosinger, Compt. rend. Soc. de biol. **112:** 557. 1933.

In the dog a group of fibers, apparently secretory, enters the hypophysis and ends in the pars intermedia, pars tuberalis, and in the islands of glandular tissue situated in the posterior lobe. These fibers arise from cells in the supraoptic, paraventricular, and inferior hypothalamic nuclei. All lesions of the tuber cinerium damage these fibers and, therefore, have an effect on the gland.

—J. C. D.

Encephalography in abnormal mental states with diabetes insipidus. Schube, P. G., J. Nerv. & Ment. Dis. **78:** 453. 1933.

A study of three cases of diabetes insipidus accompanying abnormal mental states is presented. Encephalographic studies were performed on them. The procedure in the first case alleviated the symptoms of the diabetes insipidus but accentuated the abnormal mental state; in the second case it alleviated both the diabetes insipidus and the abnormal mental state; and in the third case the diabetes insipidus and the abnormal mental state remained unchanged.

—Author's Summary.

Generalized edema occurring only at the menstrual period. Thomas, W. A., J. A. M. A. **101:** 1126. 1933. Abst., A. M. A.

The author presents two cases of generalized massive edema occurring only at the menstrual periods. He gives the results and clinical picture as he has observed them. However, the migraines of menstruation, as numerous discussions bring out, are in many respects similar. At first he felt that there was the action of a diuretic substance of the anterior lobe. This is quite opposed to the constant diuresis that occurs about three days following delivery, at the time this substance disappears from the urine. The antidiuretic principle of the posterior lobe is well known and used in diabetes insipidus. It has been suggested that this clinical picture is the antithesis of diabetes insipidus. More confusing still is the definite information, brought out recently, that this substance obtained from the urine of pregnant women is of placental, not pituitary, origin. Possibly it is another prohormone activating the anterior pituitary or opposing the antidiuretic activity of the posterior lobe. The author feels that, however complex and interrelated these processes may be, the end-results—edema and diuresis—are functions of tissue thirst, depending on hydrophilic tissue states or the reverse; that is, extrarenal factors rather than any alteration in renal function.

Pregnancy changes in the anterior hypophysis of the albino rat. Wolfe, J. M. and R. Cleveland, Anat. Rec. **56:** 33. 1933.

The anterior hypophyses of rats killed at daily intervals throughout pregnancy have been studied. During the first third of pregnancy, the relative percentage of the cells of type I (eosinophiles) was low when compared with that

of normal animals (27.1 and 32.7, respectively). The granules in these cells was reduced in number, the cells were large and took a pale stain with orange G. Throughout the remainder of pregnancy, cells of type I of this nature disappeared and a smaller cell, packed with granules, which stained intensely with orange G, appeared. There was a gradual increase in the relative percentage of the cells of type I to 32.2 on the twenty-first day of pregnancy. During the first few days of pregnancy, the cells of type III (basophiles) did not contain granular material. During the last two-thirds of pregnancy, however, these cells were packed with granules and became much larger than those found in the non-pregnant animal. On the twenty-first day of pregnancy, the non-granular form of this cell was again found. It was found that the relative percentage of the cells of type IV (chromophobes) varied inversely with the percentage of the granular cells. No "specialized pregnancy cells" were observed. Cell counts were made on all sections studied.—Authors' Abst.

Aneurysm of the internal carotid artery; report of a case simulating tumor of the pituitary. Zollinger, R. and E. C. Cutler, Arch. Neurol. & Psychiat. **30**: 609. 1933.

Aneurysms occurring at, or near, the junction of the internal carotid artery with the circle of Willis may produce changes of the sella turcica which in roentgenograms are suggestive of a tumor of the pituitary. A case is reported of a large aneurysm of the righ internal carotid artery which simulated a tumor of the pituitary in roentgenograms.—Authors' Summary.

Insulin in treatment of tuberculosis. Allen, F. M., J. A. M. A. **101**: 1798. 1933. Abst., A. M. A.

The author presents a study of more than 80 nondiabetic tuberculous patients treated with insulin. In general, he has administered more insulin than has heretofore been given to nondiabetic persons. One man received 320 units a day with rapid gain in weight, but this was an exception. Treatment was usually begun with 5 units before each meal and increased to about 40 units three times a day, but individualization should be emphasized as the chief principle. There are individual peculiarities of insulin tolerance. Women are apt to take less than men. Toxic patients usually do not stand as large doses as the nontoxic, contrary to the rule in diabetes. The same individual may differ in his insulin requirement at different times. When small doses are unsuccessful, large doses will sometimes give results and vice versa. When a patient has flourished for several weeks or months on a certain dosage and has perhaps reached normal or slightly more than normal weight, he may begin to show sensitiveness in the form of insulin reactions or nausea and may continue to thrive only after the dose has been reduced. The author has continued the administration of insulin over a period of eight months. The kind and quantity of the diet is also planned to suit the patient, but commonly a mixed diet containing liberal carbohydrate may be given, consisting of not only the usual three meals but also lunches between meals and at bedtime. In character, the author's cases ranged from mild to moribund. The majority were severe, active and febrile. Reactions are usually easy to prevent and harmless if they do occur. Fever is by no means a contraindication. Hemorrhage also need not be a contraindication, except in a minority of sensitive cases. Rarely, urticaria or other symptoms may prove troublesome, even to the extent of stopping the treatment. Intestinal lesions are more often an indication than a contraindication for insulin. The author's general conclusion from a study of his cases is that in a large proportion of tuberculosis cases ranging from quiescent to severe, the proper use of insulin can produce marked gains in weight, strength and spirits.

The use of the area of hypoglycemia in the study of the hypoglycemic action of insulin in dogs (De l'utilité des aires d'hypoglycémie dans l'étude de l'action hypoglycémiante de l'insuline chez le chien). Aubertin, E. and E. Trinquier, Compt. rend. Soc. de biol. **110**: 197. 1932.

The author analyzed his results on 30 dogs by a method involving plotting the sugar curve against time on coördinate paper. From this can be calculated the blood sugar percentage at any given time and also, by measuring the area enclosed by the curve of decrease and recovery, the total effect of different samples of insulin can be compared.—J. C. D.

Comparisons of the hypoglycemic "areas" produced by intravenous and subcutaneous injections of insulin in normal unanesthetized dogs (Etude comparative des aires d'hypoglycémie déterminées par des injections intraveineuses et sous-cutanées d'insuline chez le Chien normal en etat de véille). Aubertin, E. and E. Trinquier, Compt. rend. Soc. de biol. **110:** 968. 1932.

In 5 dogs studied, it was found that although intravenous injections of insulin sometimes caused a sharper drop in blood sugar than an equal dose given subcutaneously the latter always had the greater final influence when degree of hypoglycemia and its duration were considered.—J. C. D.

The hypoglycemic effect of insulin injected into the portal system of dogs (De l'action hypoglycémiante de l'insuline administrée dans le système porte chez le chien). Aubertin, E. and E. Trinquier, Compt. rend. Soc. de biol. **112:** 583. 1933.

In 7 fasting dogs insulin was injected into an intestinal vein. The effect on blood sugar was the same as though it had been injected into the general systemic circulation. The liver, therefore, has no direct effect on insulin.
—J. C. D.

Improvement in experimental diabetes following administration of amniotin. Barnes, B. O., J. F. Regan and W. N. Nelson, J. A. M. A. **101:** 926. 1933. Abst., A. M. A.

According to the authors, although their experiments, on dogs, clearly show that amniotin will modify glycosuria after removal of the pancreas, the explanation is not clear Tentatively, the theory is advanced that the pituitary has been suppressed, since the estrogenic substance has been found to suppress the sex principle in the pituitary. If this interpretation is correct, it would indicate that the suppression is almost complete, since the glycosuria following pancreatectomy was within the range for completely hypophysectomized dogs. It might be dangerous to suppress the pituitary completely, since other organs atrophy following hypophysectomy. This is especially true of the suprarenal cortex, which atrophies if the pituitary is removed. Before attempting to treat clinical diabetes by pituitary suppression, it will be necessary to determine whether the influence on carbohydrate metabolism can be accomplished without serious injury to other organs. This work is now under way.

Changes in the islets of Langerhans in pregnancy and other conditions. Cramer, W., Quart. J. Exper. Physiol. **23:** 127. 1933.

The islets constitute a very plastic tissue, undergoing considerable changes in a variety of physiological conditions, even to the formation of new islets, or the disappearance of existing ones. The most consistent changes are found in pregnancy, during which there is a new formation of islet tissue from the centro-acinar cells. No clear evidence has been obtained of a transformation between islet calls and acinar cells in any of the conditions studied. Prolonged exposure to heat sometimes produces degenerative changes in the islets. The significance of the results in relation to diabetes is discussed.—W. P. Kennedy.

Spontaneous hyperinsulinism; report of a case of hyperinsulinism cured by surgical intervention. Derick, C. L., F. C. Newton, R. Z. Schulz, N. A. Bowie and N. Pokorny, New England J. Med. **208:** 293. 1933.

A case is reported of an elderly woman who had recurring attacks of a syndrome typical of that following insulin overdosage. At the start of her illness 6 years previously the attacks were infrequent and of mild severity. As time progressed they became more frequent and severe so that she lost consciousness and suffered bodily harm. She found that the frequent taking of food would either prevent or abort the attacks. Physical examination revealed nothing noteworthy. Blood sugar determinations in the fasting state or during an attack revealed an abnormally low figure. The course of her illness and blood sugar values were comparable in all respects to cases previously reported in which an islet cell tumor of the pancreas was found to be the cause of the trouble. Consequently a diagnosis of islet cell tumor of the pancrease was made and later confirmed by the surgical removal of an encapsulated tumor 1.5 cms. in diameter from the pancreas. This tumor was composed of islet cells and

on biological assay had an extremely high content of insulin. The patient has remained well for three years since her operation.—C. L. Derick.

Influence of hormones on blood sugar regulation (Hormonale Einflüsse auf die Blutzuckerregulation). Elek, L., Ztschr. f. d. ges. exper. Med. **85**: 227. 1932.

One hundred pregnant women were investigated between the sixth and ninth months by the following methods: (a) 50 gm. dextrose in 200 cm. water, (b) 100 gm. dextrose in 400 cm. water, (c) twice 50 gm. at 1-hour intervals, (d) twice 50 gm. at 1½-hour intervals, administered orally in the early morning to the fasting mother. No material difference in the blood sugar curve could be determined as between pregnant and non-pregnant women. There occurred a second rise in blood sugar after the second dose of dextrose despite complete lack of the slightest evidence of insullary hypofunction. Alimentary glycosuria was noted only when the glycemic quotient reached 1.80. When folliculin was given intravenously to female guinea pigs the hyperglycemia following oral administration of dextrose was far more pronounced. The results from the anterior-pituitary-like product, "Prolan," were quite irregular. Furthermore folliculin was found to diminish sensitivity to adrenaline and increase the sensitivity to insulin.—H. L.

Staphylococcic infections in diabetes. Gilchrist, J. A. and S. L. Alexander, Canad. M. A. J. **28**: 386. 1933.

The authors believe that removal or treatment of etiological factors underlying diabetes mellitus will permit the cure of this disease in a large percentage of cases. There may be a staphylococcic factor in diabetic focal infections other than those in the upper respiratory tracts, and all foci of infection in the diabetic should be repeatedly examined for staphylococcus.—A. T. C.

The sensitization to the action of x-ray of ulcerative skin cancer by insulin locally applied (Sur la sensibilisation par l'insuline in loco, des cancers ulcérés de la peau, a l'action des Rayons X). Gomes da Costa, S. F. and F. B. Guedes, Compt. rend. Soc. de biol. **110**: 1051. 1932.

Rabbits were shaved over each rump. On one side insulin was rubbed into the skin daily and on the other water. After a month of daily treatments they were exposed to x-rays. The reaction of the insulin-treated skin was much more rapid and intense than that of the control.—J. C. D.

The use of insulin as an aid in the treatment of pulmonary tuberculosis. Heaton, T. G., Canad. M. A. J. **27**: 498. 1932.

Little or no benefit may be expected from insulin treatment in acutely active or terminal cases of pulmonary tuberculosis. Insulin is definitely useful in the treatment of chronic forms of pulmonary tuberculosis, if the patient is undernourished. The dose must be adjusted to suit the individual, the desired effect being an increased appetite without additional unpleasant symptoms. Injection should be given half an hour before the meal. A fairly large proportion of patients, however, fail to respond. Some tubercular patients react to much less insulin than will cause a reaction in normal persons. The initial dose should not exceed 5 units.—A. T. C.

The correlation between the blood-sugar fall and the initial blood-sugar in rabbits injected with insulin. Hemmingsen, A. M. and H. P. Marks, Quart. J. Pharm. & Pharmacol. **5**: 245. 1932.

In order to discover a relation between the average fall of blood-sugar during the five hours following an insulin injection, and the initial blood-sugar level, a statistical analysis has been made of the results found by injecting with insulin about 400 groups of rabbits, all the animals (4-5) within each group receiving the same dose. Half the material is derived from The National Institute of Medical Research, London, and the other half from The Laboratory of Zoophysiology, Copenhagen University. The following conclusions have been reached: (1) The absolute fall tends to increase with increasing initial values. (2) The absolute fall increases at a greater rate than the initial value, i.e., the fall expressed as a percentage of the initial value also increases with increasing initial value. (3) Different batches of rabbits give significantly

different values for the rate of increase in percentage fall with approximately 0.22 for an increase of 1 mg. per cent in the initial blood-sugar value. A method of correcting the results of tests for differences in initial blood-sugar level is suggested.—A. M. Hemmingsen.

Contributions on the physiology and pathology of the so-called kidney threshold (sugar threshold) in human beings (Beiträge zur Physiologie und Pathologie der sog. Nierenschwelle [Zuckerschwelle] des Menschen). Heténvi, G., Ztschr. f. d. ges. exper. Med. **80:** 523. 1932.

The renal threshold for glucose was determined as follows: Starting with an intravenous administration of 0.30 grams glucose per kilo body weight in 30% solution, blood sugar estimations were made at intervals of 5, 10, 15, 30 and 45 minutes after the injection. Urine was collected during the period of the experiment by means of an inlying catheter, the collecting vessel being changed every five minutes. With the above technique, the threshold was measured in human subjects before and after the administration, for a period of days, of certain endocrine agents. Twenty to 40 units of parathormone daily for 4 to 7 days was followed by an increase of approximately 30 mg. per 100 cc. in the renal threshold. Ten units produced no effect alone, but combined with a daily dose of 25 grams of $CaCO_3$ produced an increase in the threshold of similar magnitude. Calcium without the parathormone produced no significant changes. With insulin (20 or 40 units daily) there appeared to be an increase in the threshold, the validity of the experiments with insulin being questioned, however, by the author. Adrenaline (1 or 2 mg. daily for 3 to 5 days) brought about an increase in the threshold of approximately the same magnitude as parathormone. Thyroid extract (1.5 or 3 grams daily for 13 to 21 days) depressed the threshold from 12 to 50 mg. per 100 cc. A threshold below normal was observed in three cases of hyperthyroidism. Pituitrin (1 or 2 cc. daily for 3 to 5 days) increased the threshold by an amount comparable with the increase with parathormone or adrenaline.—B. S. W.

The effect of insulin and adrenaline on the excretion of nitrogen and sulfur (Untersuchungen über die Wirkung des Insulins und Adrenalins auf die Stickstoff-und Schwefelausscheidung). Jakobson, B. M., Arch. f. exper. Path. u. Pharmakol. **170:** 84. 1933. Abst., Chem. Absts. **27:** 3001.

Insulin injected into normal dogs commonly causes an increased nitrogen excretion, which cannot be due to increased protein metabolism inasmuch as the sulfur excretion is not increased. Moreover, after water diuresis insulin does not have this effect. Adrenaline may also cause an increased nitrogen excretion, but accompanied by an increased excretion of sulfur, even if hyperglycemia is prevented by the previous administration of insulin.

The high carbohydrate low fat diet for diabetic children. Jamieson, H. C., Canad. M. A. J. **27:** 389. 1932.

Good results have been obtained with a diabetic diet relatively high in carbohydrate and protein but low in fat. In many cases this diet increases the tolerance for glucose. Sugar in the urine on this diet is usually increased at first, but gradually diminishes. Cholesterol falls quickly, but may rise again to even greater heights than on high fat diets.—A. T. C.

Epilepsy and convulsions in diabetes. Jordan, W. R., Arch. Int. Med. **52:** 664. 1933.

The literature on convulsions attributed to diabetes or to its treatment has been reviewed, and pertinent data have been collected from our diabetic patients and set forth. The evidence so far tends to discredit the idea that diabetes per se causes convulsions, but it is equally evident that excessive administration of either alkali or insulin may give rise to such seizures. The appropriate literature concerning idiopathic epilepsy in persons with diabetes has been analyzed and correlated, and observations on our 22 cases have been added. The incidence of epilepsy in diabetic persons seems to be similar to the theoretical incidence in unselected people of corresponding age groups. —Author's Summary.

Insulin resistance and sensitivity. Karr, W. G., C. W. Scull and O. H. Petty, J. Lab. & Clin. Med. **18:** 1203. 1933.

A case is presented of a patient who was both very sensitive and very refractory to insulin therapy. The refractory condition has disappeared, while the sensitivity persists to some extent eighteen months after withdrawal of insulin. The patient at one time required over 600 units of insulin daily to prevent acidosis, although the fasting blood sugars were all over 200 mg. The patient has been without insulin for eighteen months, and although still diabetic is well controlled by a prescription diet. The refractory condition of the patient disappeared very suddenly about one week after the intramuscular injection of a rabbit serum, which may have contained antibodies, as the animal was sensitized to the patient's serum plus insulin.—Authors' Summary.

Adrenals and pancreatic diabetes (Suprarenales y diabetes pancreática). Lewis, J. T. and E. Turcatti, Rev. Soc. argent. de biol. **9:** 115. 1933.

The right adrenal was removed from a series of dogs; later pancreatectomy was performed and when diabetes was at its height the left adrenal was taken out. Blood sugar remained high and sometimes increased slightly after total adrenalectomy. In a few cases a slight drop in the blood sugar level was seen just before death occurred. In another series the blood sugar level was brought to normal or below by insulin treatment before taking out the second adrenal. The blood sugar rose to diabetic levels in spite of adrenal insufficiency. Glycosuria was present in all cases. It is maintained that pancreatic diabetes is not significantly modified by adrenal insufficiency.—J. T. L.

A case of glycosuria, simulating cerebral thrombosis; postmortem diagnosis—brain tumor. Macdonnell, P. M., Canad. M. A. J. **29:** 65. 1933.

A woman, aged 53, had been diagnosed as having diabetes. She developed a stuporous condition. Examination excluded diabetic coma and suggested cerebral thrombosis. Postmortem examination revealed a brain tumor (spongioblastoma multiforme) in the right frontal lobe.—A. T. C.

Insulin and the protein equilibrium of the blood serum (L'insuline et l'équilibre protéinique du sérum sanguin). Nitzescu, I. I. and D. Canciovici, Compt. rend. Soc. de biol. **110:** 65. 1932.

Twelve adult rabbits were injected and the conditions found at intervals later, compared with those found before the injection. For 1 to 2 days the total protein declines, most of the loss being in the globulins. The non-protein nitrogen also decreases.—J. C. D.

Hypoglycemic symptoms in diabetes; effect of intravenous injection of insulin. Roholm, K. and T. E. Hess Thaysen, Hospitalstid. **76:** 713. 1933. Abst., J. A. M. A. **101:** 1042.

The authors report that, after intravenous injection of 12 units of insulin, symptoms of insulinism developed in 98 of 101 attempts, or 97.3% in 80 persons with normal carbohydrate metabolism. In 82 experiments on 40 diabetic patients with intravenous injections of 12 and 24 units of insulin, insulinism was found in 19.7% and 57.1%, respectively. For development of the symptoms the blood sugar minimum must fall to about 50 mg. per hundred cubic centimeters and within about fifty minutes after the moment of injection. The kind, order, frequency and strength of the various symptoms are identical in the diabetic and the normal organism. There is no evidence of hypersuprarenalinemia in diabetes. Gastric secretion after the injection of insulin follows the same laws in diabetic as in normal persons.

Eye reactions in pancreatic diabetes. Sawyer, Margaret E., Am. J. Physiol. **106:** 491. 1933.

In experiments on cats the response of the iris (Loewi reaction) and nictitating membrane to a standard dose of adrenaline, before and after removal of the pancreas, was studied. After complete pancreatectomy a sensitization of both these structures invariably occurred. This was absent, however,

after partial excision of the gland. Denervation of the adrenal glands and liver did not influence the sensitization of the eye structures to adrenaline. Thyroidectomy only slightly diminished the increased response of the iris. The conclusion is drawn that the Loewi reaction and the sensitization of the nictitating membrane to adrenaline in diabetes are not to be explained by increased secretion of the adrenal or thyroid glands.—Author's Abst.

Bilateral splanchnic nerve section in a juvenile diabetic. de Takats, G. and G. K. Fenn, Ann. Int. Med. **7**: 422. 1933.

Bilateral splanchnic section was performed on an 18-year-old diabetic girl with the purpose of stabilizing and increasing her sugar tolerance. There has been an immediate drop to one-half of her previous insulin requirement, which seems to be due to an increase in insulin sensitivity and which has persisted up to the present writing four months after the operation. Further studies with a final report will be made at a later date.—Authors' Summary.

The association of diabetes mellitus and pernicious anaemia. Watson, E. M., Canad. M. A. J. **29**: 11. 1933.

Three new cases of this association are reported, bringing the total on record in the literature to 79. In the majority of cases the diabetes precedes the anaemia, and this is considered to be probably significant of some relationship.—A. T. C.

Decreased dextrose tolerance in acute infectious diseases. Williams, J. L. and F. Dick, Arch. Int. Med. **50**: 801. 1932.

The scope of the work included: (1) the study of acute infectious diseases in patients by means of dextrose tolerance tests; (2) the blood sugar curve of such patients; (3) the effect of the administration of dextrose and insulin on acute infections; (4) similar studies of experimental acute infections in animals. One hundred and eight patients with the following diseases were studied: scarlet fever, diphtheria, pneumonia, influenza, acute tonsillitis, measles, erysipelas, encephalitis, mumps, epidemic meningitis and poliomyelitis. Experimental infections were produced in 29 rabbits and three dogs. Temporary glycosuria occurred in 41% of the patients with acute infectious diseases when given sufficient dextrose. In six patients this decreased tolerance lasted for several weeks or months and required treatment. The decreased tolerance was improved by giving insulin. Blood sugar curves were moderately elevated and prolonged during the acute infections in both patients and experimental animals. Tolerance tests on the animals likewise revealed an increased amount of dextrose in the urine during the period of acute infection. Post mortem examination of the animals that died revealed microscopical evidence of degeneration in the islets of Langerhans. The authors conclude: (1) Glycosuria occurred in 41% of patients with acute infectious diseases. The largest average amount of dextrose was excreted by the patients with influenza and miscellaneous acute infections. (2) This glycosuria is accompanied by a lower carbohydrate tolerance as shown by dextrose tolerance tests and blood sugar curves both in acute infectious diseases and in experimental infections in animals. (3) Administration of insulin improves the dextrose tolerance in acute infections. (4) This work suggests that in infectious diseases there is often an injury to the islets of Langerhans with a lessened production of insulin.—J. L. Williams.

Simultaneous use of parathyroid hormone and calcium in abnormal uterine bleeding (Gleichzeitiges Anwenden von Nebenschilddrüsenhormon und Calcium bei krankhaften Blutungen der Gebärmutter). Bakács, G., Zentralbl. f. Gynäk. **57**: 568. 1933.

Fifty-three women having uterine bleeding (chiefly menstrual) were treated with intramuscular injections of a parathyroid extract and a preparation of calcium. The cases of menorrhagia showed especially convincing results, since the period under observation could be compared with previous periods. Subsequent menstruations, after treatment had stopped, showed a lingering prophylactic effect from the medication.—F. T. Jung.

The effect of the continuous intravenous injection of Ringer's solution on the blood chemistry of thyro-parathyroidectomized dogs. Dragstedt, L. R., R. R. Risk and Anna A. Johnson, Am. J. Physiol. **105**: 643. 1933.

The continuous intravenous injection of Ringer's solution in amounts of from 2000 to 3000 cc. per 24 hours was found to prevent the onset of tetany after complete thyro-parathyroidectomy in 7 adult male dogs but did not prevent the usual diminution in the serum calcium. These dogs were kept on an exclusive lean meat and water diet. Isolated frog muscles suspended in 0.7% NaCl solution displayed spontaneous rhythmic contractions which could be abolished by the addition of as little as 1 to 2 mgm. of calcium per 100 cc. of solution. Such muscles suspended in physiological salt solutions containing all of the inorganic salts of the serum but no calcium displayed no spontaneous activity. The relief and control of tetany obtained in these experiments by the intravenous injection of Ringer's solution may still be harmonized with the theory that the diminution in the serum calcium is the immediate cause of parathyroid tetany. It would seem to be necessary to assume, however, that it is only the ionic calcium that is physiologically active and that the administration of Ringer's solution maintains this fraction at an effective concentration in spite of a fall in the total calcium in some instances as great as 50%.
—Authors' Abst.

Contributions to the study of tetany occurring at oestrus in thyroparathyroidectomized animals; action of the gonadotropic principle from the urine of pregnancy on tetany and blood calcium in dogs (Contribution a l'étude de la tétanie de l'oestrous chez les animaux thyroparathroïdectomisés: action du principe gonadotrope de l'urine gravidique sur la tétanie et la calcémie de Chiennes thyroparathyroïdectomisées). Fredericq, H., Compt. rend. Soc. de biol. **113**: 903. 1933.

In thyroparathyroidectomized female dogs, which have attained a constant calcium level, such injections depressed the calcium and produced convulsions. In operated male dogs and bitches, which had also had their ovaries removed, the injections had no effect. In unoperated animals likewise there was no constant reaction. The ovaries were the organs through which the extract acted and, in their absence, there was no effect. In normal animals the effect was nullified by the parathyroids.—J. C. D.

Rickets and hyperparathyroidism. Hamilton, B. and C. Schwartz, Am. J. Dis. Child. **46**: 775. 1933.

A large dose of calcium chloride or calcium gluconate by mouth causes a much more marked rise in serum calcium of rachitic rabbits than of normal rabbits. The rise is generally high enough to cause the death of the rachitic animal from hypercalcemia. The authors think that this affinity for calcium in rachitic blood is due to hyperactivity of the parathyroid glands. The following test for the parathyroid hormone was applied to the blood of rachitic and normal animals: the administration of calcium chloride by mouth at intervals to normal full-grown rabbits produces a curve of serum calcium which shows a peak after the first dose and then gradually approaches the initial value. If, however, parathyroid is given previously, the curve continues to rise and reaches higher values than when no parathyroid is given. The blood from rachitic animals gave in most instances a markedly positive test while no reaction was absent with blood from normal animals. The authors conclude that blood from rachitic animals is abnormally rich in either parathyroid hormone or some other substances with identical effect on the serum calcium.—M. B. G.

A study of the number and location of the parathyroid glands in man. Heinbach, W. F., Anat. Rec. **57**: 251. 1933.

The parathyroids were studied by gross dissection supplemented by microscopic inspection in 25 human specimens. A total of 86 definite parathyroid glands was found, making an average of 3.2 per specimen. The number varied from two to six. The location of each parathyroid was determined and reported in relation to the thyroid, larynx, and trachea. An analysis was made of the variations in location which showed that 7% of the glands were opposite the cranial third of the thyroid, 57% the middle third, and 25.6% the caudal third. 10.4% were found caudal to the thyroid. One gland was found partly on the

ventral surface; none in the interior of the thyroid. It is suggested that the customary nomenclature, according to which, "there are two pairs of parathyroids, superior and inferior," with a typical location for each pair, is misleading, since no investigator, who has carefully studied and analyzed a series of cases, has found exactly four parathyroids in much more than 50% of the specimens, and since in many cases where four have been found, there is a great variation in location.—Author's Abst.

Growth, reproduction and lactation in the absence of the parathyroid glands. Kozelka, F. L., E. B. Hart and G. Bohstedt, J. Biol. Chem. **100:** 715. 1933.

Ca and P were studied in the blood and tissues of 3 litters of puppies after thyroparathyroidectomy. Vitamine D (as irradiated ergosterol in corn oil) and desiccated thyroid were given by mouth. Vitamine D repeatedly stopped attacks of tetany after longer delay, but for a longer time, than did parathormone. On a sufficient dosage of D, normal levels of blood Ca and P were maintained, and the puppies grew and reproduced normally. Overdosage with D gave hypercalcemia and toxic symptoms; but the amount required to produce such effects was greater in pregnant or lactating bitches than in other dogs. Since anything maintaining the proper levels of Ca and P enables the dog to complete a normal life-cycle, the parathyroids cannot be supposed to perform a specific and indispensable metabolic function.—F. T. Jung.

Effect of diet on response to parathyroid extract and vitamin D; the relation of calcium and phosphorus of the diet to response to parathyroid extract in rats. Morgan, Agnes Fay and Jean C. Field, Am. J. Physiol. **105:** 585. 1933.

Young rats were fed diets of high calcium-low prosphorus, normal calcium and phosphorus and low calcium-high phosphorus contents from weaning for 30 to 80 days. Half of each group were given cod-liver oil or viosterol and some of each group were injected with 60 to 90 units of parathyroid extract during the three days preceding sacrifice. Serum calcium was raised by the hormone only in the vitamin D-fed rats on the high calcium-low phosphorus diet but the inorganic phosphorus was raised in both cases with accompanying healing of rickets in the D-free group. One hundred and fifteen rats were used with this diet. On the normal diet the serum calcium was raised in the 20 rats receiving vitamin D and in the 27 without it. On the low calcium diets both groups showed hypercalcemia but the rise in serum calcium was greater in the D-free than in the D-rich animals. However, the initial level of calcium was considerably lower in the former group. Sixty-five animals were used on the low-calcium diet. A rich deposit of bone trabeculae was seen in the D-free animals on both the normal and the low calcium diets and depletion of trabeculae was seen in the D-free animals on both the normal and the low calcium diets and depletion of trabeculae was observed in all parathyroid treated rats. The conclusion is drawn that in moderate doses parathyroid extract raises serum calcium only when a good supply of calcium is available from the diet or from an accumulated reserve probably in the bone trabeculae.—A. F. Morgan.

The effect of diet on response to parathyroid extract and vitamin D; the effect of high calcium low phosphorus diets in dogs. Morgan, Agnes Fay and E. Alta Garrison, Am. J. Physiol. **105:** 596. 1933.

Nine young dogs were fed high calcium-low phosphorus synthetic diets. Marked hypercalcemia resulted in three from moderate doses of parathyroid extract when cod-liver oil or viosterol was given but little rise in serum calcium in similar animals receiving no vitamin D. However, two dogs of one litter, which had been born and reared to weaning in the country reacted to the hormone normally even though no vitamin D source was given. Healing of rickets occurred in these two dogs. Low serum calcium and inorganic phosphorus occurred in all dogs without vitamin D and normal or high calcium but low phosphorus in those given the vitamin with these diets. Addition of phosphorus to the diet raised the serum phosphate in dogs given the vitamin but not in those without it. Parallel addition of calcium to a low calcium-low phosphorus diet resulted in decreased response to parathyroid treatment especially in the dog without vitamin D. The conclusion is drawn that the source of the increased serum calcium resulting from parathyroid extract injection in moderate

dosage is the food or an easily mobilizable reserve, that the increased serum phosphate produced under these circumstances may heal rickets and that the level of serum phosphate is governed not only by the dietary level but also by the Ca:P ratio whether vitamin D is present or not.—A. F. Morgan.

The effect of diet on response to parathyroid extract and vitamin D; the effect of low calcium-high phosphorus diets in dogs. Morgan, Agnes F., E. Alta Garrison and Marguerite J. Hills, Am. J. Physiol. **105**: 608. 1933.

A low calcium-high phosphorus synthetic diet of calcium to phosphorus ratio 0.1 without vitamin D produced severe bone deformities, tetany, and muscular paralysis in 7 of 8 young dogs. Even when supplemented by 1 or 2 grams of potent cod liver oil per kilogram per day this diet brought about similar but less severe symptoms in 3 of 5 young dogs. The dogs without cod liver oil had low serum calcium and low or normal inorganic phosphate but those given cod liver oil showed normal values. The first doses of parathyroid extract (90 units in three days) stimulated slight hypercalcemia in all except one large dog. Further administration, however, produced little or no effect unless the dose was greatly increased. The rise in serum calcium was nearly the same in the small dogs whether vitamin D was present or not but was very low in the one large dog without vitamin D. The addition of cod liver oil caused better retention of calcium in the one dog examined than was secured without it in two similar dogs. Parathyroid extract in doses of 30 units daily (about 4 units per kgm.) caused little change in calcium retention but lessened phosphorus retention in both the dog which received vitamin D and the dog which did not. The ratio of calcium to phosphorus in the feces of the dog which received vitamin D is seen to be the same as that of the diet but is considerably higher in the feces of the two dogs which received no vitamin D.—Authors' Summary.

Effect of diet on response to parathyroid extract and vitamin D; the effect of diets of normal calcium and phosphorus content in dogs. Morgan, Agnes Fay, E. A. Garrison, F. Gillum and M. J. Hills, Am. J. Physiol. **105**: 621. 1933.

Young dogs fed a normal synthetic diet showed hypercalcemia on treatment with parathyroid extract only when vitamin D was also given, but adult dogs responded to the hormone equally with and without the vitamin. When ammonium chloride was given the hypercalcemia resulting from moderate doses of the parathyroid extract was lessened while on addition of sodium carbonate it was increased. Calcium and phosphorus retention was the same with and without vitamin D but parathyroid treatment decreased P retention in the D-fed animal. Sixteen dogs were used in these tests. In another experiment three pairs of young dogs were fed diets of high, normal and low Ca:P ratio, one of each pair being given viosterol. All were given parathyroid extract at the same time, with resulting death from overdosage in all three which received the vitamin. The conclusion is drawn that these and the other dogs reacted as might be expected if the response to parathyroid hormone is dependent upon the presence of a calcium reserve. The vitamin is thought not to act by stimulation of the parathyroid glands nor in moderate dosage to strip essential bony structures.—A. F. Morgan.

A case of parathyroid tetany with normal chronaxie and gastric spasms (Un cas de tétanie parathyréoprive [chronaxie normale, spasmes gastriques pendant l'accès de tétanie]). Mussio-Fournier, J. C., A. Garra and C. A. Castiglione, Bull. et méd. d. hôp. de Paris, **30**: 1. 1933.

A married woman, age 47, had been operated upon for cystic goiter. The complaint was tetanic attacks. The serum calcium was low, B.M.R. —3%, Chvosteck's sign positive, and Trousseau's sign positive. The chronaxie of the arm muscles between tetanic attacks was normal. During attacks, the chronaxie was very slightly augmented. Actinograms of the stomach during an attack of tetany showed spasms of this organ. Treatment with parathyroid hormone (Collip), 10 units subcutaneously three times a week, produced the following results: the spontaneous contractures of the muscles disappeared, the serum calcium was elevated, the stomach spasms disappeared and the signs of Trousseau and Chvosteck were no longer positive.—E. L.

Parathyroid dysfunction; report of case treated with parathormone and irradiated ergosterol. Ortenberg, S., Canad. M. A. J. **28**: 490. 1933.

Generalized osteodystrophy is reported in an elderly male, with x-ray characteristics of osteitis fibrosa cystica, but with a normal blood calcium. Traumatic fractures remained ununited for 4 months, in spite of rest, immobilization, and the use of viosterol, cod liver oil, and 60 grains of calcium daily. Moderate doses of parathormone produced rapid formation of callus, restoration of the bony architecture, and rapid resorption of pitting oedema.—A. T. C.

Influence of extirpation of one external parathyroid on the lipoid contents of the corresponding undisturbed gland (Influence de l'extirpation d'une parathyroïde externe sur la teneur en lipoïdes de la glande symétrique restée en place). Parhon, C. I. and E. Cernautzeanu-Ornstein, Compt. rend. Soc. de biol. **109**: 1395. 1932.

One external parathyroid was removed from each of 9 rabbits. The corresponding gland was examined from 3 days to 3 weeks after operation. In 8 animals the gland left in place was richer in lipoids than the removed gland. The form of the lipoid varied, being either that of isolated droplets or fine granulations but was always the same in the extirpated and the undisturbed gland. The lobe of the thymus on the operated side shrank.—J. C. D.

Morphological changes in the parathyroid glands of rabbits during poisoning with sodium fluoride (Les altérations morphologiques des glandes parathyroïdes dans l'intoxication expérimentale par le fluorure de sodium chez le lapin). Pavlovic, R. A. and D. M. Tihomirov, Compt. rend. Soc. de biol. **110**: 497. 1932.

Rabbits poisoned with sodium fluoride were examined, some at 2 days and some at 105-156 days. The parathyroids of the acute cases showed parenchymatous degeneration with numerous hemorrhages, while the chronic cases showed fatty degeneration with very few hemorrhagic areas.—J. C. D.

Chemical studies on a parathyroid hormone. Tweedy, W. R. and M. Torigoe, J. Biol. Chem. **99**: 155. 1932.

The paper represents an attempt to identify the physiological activity of the hormone with the presence of definite chemical groups in the "hormone" molecule. Reversible inactivation after inactivation by formaldehyde is interpreted as strongly indicative of a nitrogen containing group—probably an amino group. Reversible inactivation after inactivation with acid methyl alcohol is less positively interpreted as indicative of an essential carboxyl group. Adsorption by permutit is attributed to the presence of amino nitrogen groups in the protein-like substance with which the hormone activity is closely identified.—Authors' Abst.

Relation between thymocrescin and thyroxine in the growth of animals (Die Beziehungen zwischen Thymocrescin und Thyroxin beim Wachstum der Tiere). Nowinski, V. W., Biochem. Ztschr. **259**: 182. 1933. Abst., Chem. Absts. **27**: 2722.

The thymus apparently produces two specific substances, one relieving fatigue, the other stimulating growth. When the latter, the thymocrescin, is given together with thyroxine which has a somewhat stimulating effect on general body growth, the action is not a summation but rather a mutual inhibition. The action on the gonads, however, is different. The gonad growth is also stimulated by thymocrescin, but the effect of the combination of thymocrescin with thyroxine is even greater.

Simple goiter; the incidence of thyroid enlargement in Winnipeg school children. Abbott, A. C., Canad. M. A. J. **27**: 146. 1932.

Thyroid enlargement is endemic in Winnipeg, as shown by its equal distribution in girls and boys. The incidence in boys tends to decrease after 12, and that in girls to increase, suggesting that puberty has a much more profound effect in girls than in boys. Slight thyroid enlargements should be regarded as physiological, but are best kept under observation by a physician. Medium and

large sized thyroid enlargements should be regarded as pathological and treated as such. The prevalence of goiter in Winnipeg is greater in those districts inhabited by peoples of foreign extraction. Prophylactic thyroid therapy has apparently reduced the incidence of thyroid enlargement in this city more than 50% in 4 years. The widespread use of iodized salt is possibly one of the greatest factors in the decrease.—A. T. C.

Simple goiter; its racial incidence and its relationship to nutrition. Abbott, A. C., Canad. M. A. J., **27**: 236. 1932.

Survey of Winnipeg school children shows that thyroid enlargement is much more prevalent in those of Central European parentage and Jewish children than others. The diets of English, Irish, Scottish, Welsh and Icelandic children are well balanced, and thyroid enlargement in these children is less than half that found in the other national groups examined. Cabbage is a predominant constituent of the dietary of the central European races among which thyroid enlargement is very prevalent. The diets of Jewish children are poorly balanced and are rich in fat. This may be a predominating factor in determining the large number of goiters amongst these children. Underweight apparently is not a factor.—A. T. C.

Simple goiter; the relationship between chronic foci of infection and simple thyroid enlargement in children. Abbott, A. C., Canad. M. A. J. **27**: 376. 1932.

The incidence of thyroid enlargement is slightly greater in children with septic teeth and tonsils than in otherwise normal children.—A. T. C.

The effect of tracheal compression on the thyroid gland. Abbott, A. C., A. M. Goodwin and Sara Meltzer, Canad. M. A. J. **28**: 481. 1933.

The thyroid gland in young animals (dogs, cats) is normally hyperplastic. This is more evident in kittens than in pups. The adolescent thyroid in children is therefore probably hyperplastic and not colloid. Experimental tracheal compression, reducing the size of the trachea to one-eighth, causes a reversion of a hyperplastic gland to the colloid state. Such tracheal compression is more effective in young animals than in adults.—A. T. C.

The production of hyperplasia of the thyroid with hyperthyroidism in the albino rat. Anderson, Evelyn M., Canad. M. A. J. **28**: 23. 1933.

The thyroid of the rat appears to be resistant to the influence of anterior pituitary extracts. An alkaline extract of anterior pituitary gland, together with subcutaneous injections of killed staphylococcus aureus given in gradually increasing doses of 1.2 million up to 1200 million seems to have no demonstrable effect on the thyroid apparatus, but one to three intraperitoneal injections of staphylococcus aureus in doses of 1.2 million to 12 million in conjunction with an alkaline extract of anterior pituitary will produce in the rat in 4 to 10 days a marked rise in the basal metabolism and an increase in the weight of the thyroid with a severe hyperplasia.—A. T. C.

Significance of iodine content of human blood. Curtis, G. M., C. B. Davis and F. J. Phillips, J. A. M. A. **101**: 901. 1933. Abst., A. M. A.

The authors observed that a relation exists between the activity of the thyroid and the metabolism of iodine which is undeniable. The iodine content of human blood is thus a measure of thyroid function. Demonstrable changes in the level of the blood iodine accompany those diseases in which thyroid function is altered. The fluctuation of the blood iodine during the course of thyroid disease under management is significant. The blood iodine is increased in thyroid hyperfunction. It is lowered in thyroid hypofunction. It is always elevated by any form of iodine medication. It would seem that the level of the blood ioidine is controlled by thyroid activity. There are corresponding changes in the urinary excretion of iodine. This increases in thyroid hyperfunction. It likewise is increased on any form of iodine medication. Simultaneous investigation of the basal metabolic rate, the level of the blood iodine and the urinary excretion of iodine reveals significant evidence of thyroid activity. The significance of the blood iodine in thyroid disease is similar to that of the blood sugar in diabetes mellitus and to that of the blood calcium in parathyroid disease.

Influence on the milk secretion of goats of extirpation of the thyroid (Beitrag zur Kenntnis des Einflusses der Schilddrüsenexstirpation für sich allein, bei Nachbenhandlung mit Hypophysen-Vorderlappen-Gesamtextrakt und bei Vorbehandlung mit Placentaextrakt und Corpus luteum-Brei auf die Milchsekretion von Ziegen). Fellenberg, T. and F. Grüter, Biochem. Ztschr. **253:** 42. 1932.

The phosphorus-calcium ratio in goats' milk, normally varying within narrow limits, was increased following thyroidectomy (2 goats). The phosphorus content was lowered moderately, the calcium markedly. The chloride content was increased, and the total ash became more acid. Administration of anterior lobe increased the mineral content of the milk, in normal or thyroidectomized animals, without alteration of the phosphorus-calcium ratio. Placenta and/or corpus luteum extracts produced no definite changes.—B. S. W.

Masked thyrotoxicosis simulating primary neurosis. Ginsburg, S., J. Nerv. & Ment. Dis. **76:** 331. 1932.

Six cases are presented and the literature is reviewed. From these data it appeared that thyrotoxicosis affects persons of all ages from early infancy to advanced old age. Emotional shock and strain—biologic, social-economic or sexual traumatic—in apparently normal or neuropathic individuals may lead to the clinical development or exacerbation of atypical thyrotoxicosis. Marked thyrotoxicosis may exist for many years without any thyroid enlargement or exophthalmos. The constitutional symptoms of thyrotoxicosis resemble closely the manifestations of the neuroses and, in the absence of thyroid enlargement and exophthalmos, have been mistaken for pure neuroses. Many a case of "neurocirculatory asthenia" as well as "nervous indigestion" has been proven to be thyrotoxic in origin. A depressive psychosis may develop in definite dependence upon toxic thyroid products. Such a psychosis has cleared up and failed to recur when the thyrotoxic condition was controlled. When confronted by a case of neurosis or depressive psychosis associated with tachycardia, tremor, heat tolerance, excessive sweating, loss in weight, diarrhea with or without abdominal cramps, with or without thyroid enlargement—the possibility of thyrotoxicosis should be investigated. The most valuable single corroborative laboratory test when positive is the presence of an increased basal metabolic rate. However, one must remember that in atypical or "borderline" cases of thyrotoxicosis the basal metabolic rate may be only slightly raised or normal. In doubtful cases the iodine-therapeutic-diagnostic test—marked amelioration or aggravation of symptoms after iodine medication—may be greatly helpful in the diagnosis. Similarly, clinical improvement following radium application over the thyroid speaks in favor of an underlying thyrotoxicosis.

—Author's Abst. (abbreviated).

The weight of the thyroid gland in the Belgian low-lands (Le poids de la glande thyroïde dans la basse Belgique). Goormaghtigh, N., Compt. rend. Soc. de biol. **112:** 217. 1933.

From the weights of the glands found at 400 autopsies, the author plots a curve of thyroid growth, which is parallel, generally speaking, with curves based on gland weights from 4 other localities. While the Belgian glands were smaller, they followed the same growth rhythm.—J. C. D.

The life line of the North American thyroid gland (Die Lebenskurve der nordamerikanischen Schilddrüse). Hellwig, C. A., Endokrinologie, **12:** 323. 1933.

Comparative morphologic studies of normal thyroid glands have been made in this country in only three regions, namely, in Chicago, in Minneapolis and in Kansas. The gross and histological findings in 1600 "normal" North American thyroids were compared with European material and the weight, size of the acini, presence of hyperplastic changes and the frequency of nodules were considered. North American thyroids from goiter-poor (Kansas) and goiter-rich (Minnesota, Illinois) regions do not show as marked differences in size and structure as do the European glands. The average weight of the thyroid gland in the adult varies in North America between 20.0 and 27.8 grams. Congenital goiter was not observed by the three observers; 13.9% of the adults in the Wichita material had a thyroid weight higher than 35 grams. The average size of the acini in North American glands is relatively large and after the 35th year of life it exceeds that in North German material. Of the adult thyroids

in Wichita, 15.8% showed mild acinar proliferation and about one-half the "normal" North American thyroids of adults contained circumscribed nodules. The North American thyroid gland resembles that of the plains regions of Europe—Northern Germany, Holland, and the Russian lowlands—and differs markedly from the normal thyroid gland of Switzerland as described by Isenschmidt, Sanderson-Damberg and Schaer.—Author's Abst.

Pituitary and thyroid activity in relation to basal metabolism (Acci'n de la hipófisis y la tiroides sobre el metabolismo basal). Houssay, B. A. and A. Artundo, Rev. Soc. argent. de biol. **9:** 66. 1933.

Basal metabolism was determined in 5 hypophysectomized dogs and a 12.6% decrease, as compared with 5 normals, was found. Thyroidectomy after hypophysectomy produced a further decrease to 22.2% below normal. Thyroidectomy alone produced a 24.1% decrease. It is maintained that the pituitary influences basal metabolism through its action on the thyroid.—J. T. L.

Hypophysis and thyroid; hypophysis and compensatory hypertrophy of the thyroid (Hypophyse et thyroïde. Hypophyse et hypertrophie compensatrice de la thyroïde). Houssay, B. A., A. Biasotti and A. Magdalena, Compt. rend. Soc. de biol. **110:** 142. 1932.

Six dogs were hypophysectomized, the tuber cinereum was injured in 5 others, and 6 were used as controls. Each of these animals was subjected to a subtotal thyroidectomy. In the controls and those with tuber injuries there was the usual marked hypertrophy of the follicular epithelium in the thyroid left in place. In the hypophysectomized animals the epithelium showed no evidence of hypertrophy. The ability of thyroid tissue to hypertrophy in response to a deficiency is, therefore, dependent on the presence of the hypophysis.—J. C. D.

Hypophysis and thyroid; extracts of the anterior lobe of the hypophysis and susceptibility to lack of oxygen (Hypophyse et thyroïde. Extrait de lobe antérieur d'hypophyse et sensibilité a l'anoxémie). Houssay, B. A. and C. T. Rietti, Compt. rend. Soc. de biol. **110:** 144. 1932.

Twenty-eight white rats were given injections of Evans and Simpson alkaline extract. Thirteen of these had been previously thyroidectomized. Their resistance to loss of oxygen was compared with that of controls by use of a beli jar from which the air was gradually exhausted. The thyroidectomized animals died last, the intact injected animals first. Increased susceptibility to lack of oxygen is recognized exidence of increased thyroid activity. This increase, as shown in rats injected with hypophyseal extract, is, therefore, dependent on the stimulation of the thyroid.—J. C. D.

Blood cholesterol in thyroid disease; effect of treatment. Hurxthal, L. M., Arch. Int. Med. **52:** 86. 1933.

The author presents further evidence in support of the theory that there is a reciprocal relationship between the basal metabolic rate and the level of blood cholesterol. Using average values as a basis there is shown to be a decrease in the basal metabolic rate after subtotal thyroidectomy and a coincident increase in blood cholesterol. An examination of the data reveals, however, that with a basal rate between 0 and —10, cholesterol values ranging from 97 to 250 mg. were obtained, while with basal rates between +60 to +70, cholesterol values from 96 to 199 were found. In one group of 25 cases on admission, the average cholesterol value was 123.5 mg. and the basal metabolic rate was 40.5, while in a second group of 19 cases, with a basal rate of +60, the cholesterol value was 124 mg. The blood cholesterol which is low in toxic states is brought to a normal level partly by pre-operative treatment but chiefly by sub-total thyroidectomy.—J. M. Looney.

Inheritance of sporadic goiter. Kemp, T., Hospitalstid. **76:** 503. 1933. Abst., J. A. M. A. **101:** 416.

The author reports a family with seven or eight cases of sporadic goiter in three generations, all in women and appearing between the sixteenth and the forty-fifth year, the symptoms of exophthalmic goiter in one instance presumably having developed some years after the simple goiter. He says that of

the families with sporadic goiter on a genotypical basis reported in the literature a number resemble this family and that the inheritance can be explained on the assumption that the disturbance depends on a dominant factor, present in the X chromosome, which causes not only development of goiter but also nondisjunction of the two X chromosomes in women. It can also be explained if the disorder is dependent on several genes of like action and is limited in sex to women.

The stillbirth problem in relation to iodine insufficiency. Kemp, W. N., Bull. Vancouver Med. Assoc., Pp. 1-8, December, 1933.

The author was impressed with the fact that a large proportion of the calves and colts born in the vicinity of Vancouver died at birth unless the mothers were given iodine during the gestation period. In that case the condition was entirely corrected. He was led to make a statistical study of stillbirths occurring in Vancouver hospitals over the preceding three to five years. The exclusion of stillbirths of recognizable cause left 91 in one series. Of these, six or 0.27% of total births in the series occurred in the practices of physicians who routinely prescribed iodine during gestation. The remaining 78 or 0.54% of total births in the series occurred in the practices of physicians who routinely prescribed iodine during gestation. The remaining 78 or 0.54% of the total births represented occurred in the practices of physicians who seldom prescribed iodine prenatally. Other statistics are cited which support the conclusion that there is an important relationship between prenatal iodine deficiency and the incidence of stillbirths. The prophylactic use of iodine is strongly recommended.—R. G. H.

On the iodine content of the thyroid gland in the human foetus, newborn and suckling (Über den Jodgehalt der fetalen, Neugeborenen—und Säuglingsschilddrüsen). Lelkes, Z., Endokrinologie, **13**: 36. 1933.

The literature reveals that a considerable number of investigators have reported total absence of iodine in the human fetal thyroid gland, while others found iodine present occasionally. In contrast to these reports several authors invariably identified the halogen in fetal glands. It has also been shown that the iodine complex in thyroid of new born was physiologically active on tadpole metamorphosis. The present investigation was carried out in an effort to clarify these apparent contradictions. Twenty-five fetal thyroid glands, three thyroids from new born and six from sucklings were examined, both histologically and chemically. The findings are tabulated and show the number of glands investigated, age and sex, size and weight, absolute and relative iodine content, season when collected, as well as clinical and diagnostic remarks. Iodine was present in all the thyroids investigated beginning with the four months of pregnancy. A sharp decrease in size of the thyroid was observed during the first few post natal weeks and a very marked increase in the absolute and relative iodine content. In general, the glands collected during the winter months contained more iodine than the summer glands. No parallelism was found to exist between the iodine content and the amount of colloid present in the glands either before or after birth as claimed by some investigators. The amount of iodine in the fetal thyroid does not seem to be less in areas where endemic goiter is prevalent than in other goiter-free regions. While this investigation does not give a final picture of the iodine compounds and the function of the embryonic thyroid, it may be definitely established that the fetal gland selects and stores iodine from the beginning of the fourth month of pregnancy. The possibility of a limited hormone activity of the fetal thyroid during the latter part of intrauterine life in correlation with the maternal organ is proposed.—F. Fenger.

Cardiovascular symptomatology in exophthalmic goiter. Lerman, J. and J. H. Means, Am. Heart J. **8**: 55. 1932.

Analysis of 184 cases of toxic goiter is made, using 233 cases of non-toxic goiter as a control. Cardiac symptoms are more common in the female than in the male patients with hyperthyroidism. The severity of the symptoms is greater and their duration longer in the female than in the male patients. Cardiac enlargement, precordial thrill and a superficial pericardial friction rub are more common in the female toxic patients, whereas auricular fibrillation

and other forms of arrhythmia are more common in the male. The incidence of organic heart disease is the same in the toxic group as in the non-toxic group, i.e., 13%. The pulse rate tends to be slower in the male than in the female hyperthyroid patients, while the pulse pressure is higher. It may be inferred that the demands on the circulation are met by different mechanism: in the female chiefly by increasing the heart rate, and in the male chifly by increasing the output per beat. The frequency of the symptoms of dyspnea and palpitation and their severity are influenced by various factors, such as obesity, undernourishment, cardiac enlargement, fibrillation, other arrhythmias, precordial thrill, valvular disease, other organic cardiac disease, pericardial friction rub, level of metabolism, pulse rate and pulse pressure. On the other hand, they are not influenced by age, size of thyroid and peripheral arteriosclerosis. Cardiac disease in hyperthyroidism takes the form chiefly of auricular fibrillation, angina, or congestive failure, whereas in non-toxic goiters it takes the form of hypertensive and arteriosclerotic heart disease. Hyperthyroidism per se does not produce thyroid heart disease, but produces functional derangement in a previously damaged cardiovascular system. A superficial pleuro-pericardial friction rub heard over the sternum in toxic goiter patients is described.

—J. Lerman.

Hypophysis and thyroid; effect of ablation or implantation of the thyroid on the hypophysis of toads (Hypophyse et thyroïde. Action de l'ablation ou de l'implantation de la thyroïde, sur l'hypophyse du crapaud). Magdalena, A., Compt. rend. Soc. de biol. **112:** 489. 1933.

The title is in error since the hypophyses were removed or implanted. As the result of the examination of 70 adult toads, the anterior lobe was found to be the controlling factor for the thyroid; loss of it caused atrophy and implants caused stimulation of this gland. Other parts of the hypophysis and other organs did not influence the thyroid.—J. C. D.

Observations on the structure of the blood vessels within the thyroid gland of the dog. Modell, W., Anat. Rec. **55:** 251. 1933.

The arteries in the thyroid glands of puppies and adult dogs were studied. In the main, thick (45 micra) frozen sections were stained according to the Cajal silver nitrate, pyridine and alcohol technique. Several serials stained with hematoxylin and eosin were studied and some glands were injected with fine silver precipitates. It was possible because of the thick sections used, and the specificity of the Cajal technique for smooth-muscle and endothelial cells, to follow entire arteries for some distance in the same section. Muscular cushions were found in the smaller arteries directly under the endothelium, situated at the point of branching. These were often large enough to act as valves and to partially or completely occlude the lumina of the vessels. Direct arterio-venous anastomoses were demonstrated. Some of these were of the magnitude of capillaries and had no muscle coats, others were larger and the muscle coat was complete up to the point of union with the vein. It is suggested that these structures may function to regulate the amount of blood flowing through the arterial branches and capillary beds of the follicles and in this manner control the amount of absorption of the thyroid hormone.

Childhood myxedema (Ueber kindliches Myxödem). Noble, E. and A. Ronald, Wien. klin. Wchnschr. **461:** 897. 1933.

Observations and investigations based on ten years of experience with childhood myxedema are recorded. Thyroid medication in childhood myxedema is specific. Some of the poor results are due to the variability in strength of commercial thyroid preparations, so that dosage is not uniform. In order to use thyroid as a therapeutic agent it is necessary to solve two problems: (1) The activity of the thyroid; (2) the optimum dose of a standardized product. The authors used a method of assaying thyroid activity, which consisted in determining the amount lethal to guinea-pigs. The results were parallel to the thyroxine content of the preparations. Numerous clinical studies of cretins were made, such as body development, temperature, pulse, basal metabolism, specific dynamic action, water metabolism, etc. Electrocardiographic changes described by Zondek were studied. They determined that there exists a relationship between the amount of thyroid ncessary and the sitting-height of the

patient, and cite a table of dosages depending on this measurement. The results of treatment depend upon the time when treatment is begun, and the length and the regularity of treatment. Mental improvement occurs as well as physical improvement, although they do not always run parallel.—J. Lerman.

Has insulin an effect on the thyroid gland (Wirkt das Insulin auf die Gl. thyroidea)? Räihä, C. E. and U. Uotila, Skandinav. Arch. f. Physiol. **65**: 287. 1933.

Rabbits received relatively large subcutaneous injections of insulin for about one month. They were then killed and the thyroid glands were fixed in Zenker-formol and stained by Bensley's method. The following histologic evidences of thyroid hyperfunction were found: disappearance of stainable intrafollicular colloid; hypertrophy of thyroid epithelium; nuclei large and poorly stained; appearance of unstainable vacuoles and of so-called secretory granules in the cytoplasm; and hyperemia. In rabbits which died with hypoglycemia during the insulin treatment, the hyperemia was extreme and the reddish cytoplasmic granules very numerous. One month after discontinuing the insulin, the thyroid gland follicles appeared full of red-stained colloid; the cells and nuclei were smaller and more deeply stained, with numerous unstained cytoplasmic vacuoles.—C. M. Jackson.

Cyanogen metabolism;thyroid gland activity and lack of oxygen (Cyanstoffwechsel; Schilddrüsenwirkung und Sauerstoffmangel). Schechter, M., Ztschr. f. d. ges. exper. Med. **84**: 424. 1932.

In vitro experiments previously reported by the author demonstrated that the combining power of liver tissue for cyanic acid was decreased in animals previously treated with thyroxine. In the present article experiments are described which indicate that thyroxine-treated animals, or those treated with the serum of patients with hyperthyroidism, tolerate oxygen deprivation less effectively than controls. Mice and rats were placed under a bell jar at atmospheric pressure. Carbon-dioxide was absorbed by a pan of alkali solution and the oxygen utilized was replaced by adding hydrogen. Eight mice that had received 0.01 mg. thyroxine per kilogram of body weight 2 to 5 days previously survived from 42 to 82 minutes as compared to 100 to 150 minutes for 7 controls. The shortest survivals occurred with the animals injected 3 days previously. Four rats, similarly treated with thyroxine, lived 73, 80, 130 and 130 minutes, respectively, compared to 165, 190 and 196 minutes for 3 controls. In 6 other experiments with 8 rats, analyses of the air in the bell jar at the time of the animals' death, revealed from 2.08 to 2.37% for the normal controls and from 3.4 to 6.8% for the animals given thyroxine. Similar observations of Streuli and others are mentioned. The survival times in the bell jar for 11 mice injected with the serum of patients with hyperthyroidism (3 x 1.0 cc. serum every 2 days) were from 40 to 67 minutes, but low survival times also occurred in some of the control animals in this experiment (one, 70 minutes) and in animals injected with serum from patients with other diseases (one, a case of angina pectoris, 55 minutes; a patient with icterus, 57 minutes, etc.) There was no evident relationship between the height of the basal metabolic rates of the patients with hyperthyroidism and the survival time of the mice injected with their sera. The article suggests that the diminished resistance to oxygen deprivation of thyroxine-treated animals is paralleled by the diminished cyanic acid combining power of the tissue of such animals, suggesting that both processes depend on some substrat such as the carbohydrate reserves.
—R. M. Wilder.

The iodine and bromine content of the thyroid (Untersuchungen über den Jod— und Bromgehalt der Schilddrüse). Tanino, F., Biochem. Ztschr. **241**: 392. 1931.

Twelve thyroids, classified on the basis of small, moderate or abundant amount of "colloid," were analyzed for water content, iodine, and bromine. The percentage of water was greatest in the group with small colloid content, varying from 76.5 to 81.1; the limits for the medium group were 72.8 and 75.2, and for the group with abundant colloid 71.3 and 73.1. The limits of bromine (in milligrams per cent) found in the three groups, respectively, were 11.42 to 31.27, 18.45 to 53.45, and 22.67 to 49.18. In the same units for iodine, the figures are 1.05 to 4.57, 1.43 to 3.89 and 1.90 to 2.43. The ratio of bromine

to iodine varies for the three groups, respectively, within the following limits: 5.9 and 10.8, 7.0 and 27.3, and 11.9 and 20.2. These glands were all autopsy material from subjects without thyroid disease. Seven thyroids removed at operation from patients with definite Basedowian symptoms analyzed as follows: water content, 72.5 to 80.3%; bromine, 4.20 to 25.25 mg. per cent; iodine, 5.93 to 9.37 mg. per cent; bromine to iodine ratio, 0.7 to 3.65. Samples of "colloid" removed from cystic glands analyzed as follows: bromine, 1.82 to 17.40 mg. per cent; iodine, 1.38 to 13.45 mg. per cent; bromine-iodine ratio, 0.2 to 3.5. The authors call attention to the striking variation in the composition of the "colloid," as far as bromine and iodine are concerned, and to the fact that the composition of the colloid bears little relation to the analytical results obtained with the whole gland.—B. S. W.

Clinical and experimental studies of goiter problem and of exophthalmic goiter (Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit). Schneider, E. and E. Widmann, Deutsche Ztschr. f. Chir. **241:** 15. 1933. Abst., J. A. M. A. **101:** 1039.

The authors, in the present study, found that liver damage of thyrogenous origin was characterized by diminution in glycogen content, a sign of an increase in the rate of breaking up of carbohydrates. In contradistinction to toxic liver damage, it was not accompanied by fatty infiltration, so that the law of isodynamic substitution did not hold true in this instance. Toxic liver damage in ileus is characterized by changes in the concentration of blood ions with a resulting hypochloremia and hypocalcemia, while the sodium ions remain undisturbed. In the thyrogenous liver damage there is, to the contrary, a lowering of sodium ions, while chlorine and calcium ions remain unaltered. The authors subjected certain preoperative methods to a critical study by first producing an experimental state of exophthalmic goiter by means of hormone influence, controlling the picture by histologic studies, by determination of blood ions, especially of sodium and chlorine ions, and by determination of glycogen and fatty acids as well as of mineral salts in the liver and muscles. The general favorable clinical experiences with iodine as a preoperative measure were confirmed by experiment. The disturbed action of the thyroid gland, resulting from the administration of the thyrotropic hormone, and the consequent liver damage were almost completely controlled by proper doses of iodine in a ten-day experiment. Plummer's method was able to prevent the development of experimental exophthalmic goiter. Diiodotyrosin influenced the histologic picture but did not prevent liver damage. The authors consider it much inferior to iodine. Casein is desirable and is easily administered in the form of curds, but it has little influence as a preoperative measure.

Monosodium thyroxine, desiccated thyroid and an impure sodium salt of thyroxine; comparison of their effects when administered orally with the effect of thyroxine injected intravenously in an alkaline solution. Thompson, W. O., Phebe K. Thompson and Lois F. N. Dickie, Arch. Int. Med. **52:** 576. 1933.

In six patients with myxedema whose basal metabolism varied from minus 18% to minus 41% (average, minus 30%) during the period of myxedema, it was necessary to administer from 0.40 to 1.46 mg. (average, 1.1 mg.) of the monosodium salt of thyroxine daily by mouth in order to hold the basal metabolism at the normal level. In the two patients in whom a comparison of the daily maintenance dose was made, it was noted that the effect of the monosodium salt by mouth was only from one-quarter to one-fifth as great as that of thyroxine given intravenously in alkaline solution. Pure synthetic thyroxine had much less effect by mouth than its monosodium salt. Squibb's thyroxine for oral use had an effect greater than that of the monosodium salt and less than that of thyroxine given intravenously in alkaline solution. Thus in four patients whose basal metabolism varied from minus 31% to minus 41% (average, minus 35%) during the period of myxedema, it was necessary to administer from 0.46 to 0.73 mg. (average, 0.63 mg.) daily of this product in order to hold the basal metabolism at the normal level. In all four patients the effect of this substance was from two to two and one-half times as great as that of the monosodium salt by mouth, while in the two patients in whom the comparison was made, it was only about one-half as great as the effect of thyroxine given intravenously in an alkaline solution. We have previously reported

that in the first two patients of this study the effects of desiccated thyroid by mouth and thyroxine intravenously or subcutaneously were the same on the basis of equivalent iodine contents. In the digestion of desiccated thyroid, peptides and polypeptides of thyroxine are formed which have a wide range of solubility. The solubility of thyroxine compounds appears to be a factor in their absorption from the gastro-intestinal tract and hence in their effect on the basal metabolism.—Authors' Summary.

Effect of alkali on the absorption of thyroxine from the gastro-intetstinal tract; with a note on the comparative effects of synthetic and "natural" thyroxine injected intravenously. Thompson, W. O., Phebe K. Thompson, Lois F. N. Dickie and J. M. Alper, Arch. Int. Med. **52:** 809. 1933.

In three patients with myxedema, single doses of 7.5 and 10 mg. of synthetic thyroxine in an alkaline solution had from 68 to 80% as much effect on the basal metabolism when administered by the mouth as when injected intravenously, in terms of the increase in basal metabolism and from about 72 to 84% as much effect in terms of excess calory production. The same doses given by mouth in the form of the monosodium salt to two patients had only from one-third to two-fifths as much effect as an alkaline solution given by mouth. In one patient a single dose of 10 mg. of pure synthetic thyroxine by mouth produced too slight a change to be measured. The solubility of any thyroxine compound administered appears to play an important rôle in its absorption from the gastro-intestinal tract and hence in its effect on the basal metabolism. In two of the patients the intravenous injection of synthetic thyroxine produced approximately the same increase in basal metabolism as an equal dose of "natural" thyroxine.—Authors' Summary.

Cholesterol partitions of the blood in myxedema (cretinism). Schwarz, H. and A. Topper, J. Pediat. **3:** 242. 1933.

This paper reports the result of a study of the proportion of free cholesterol to ester in 11 cases of myxedema. Cholesterol appears normally in the blood in the free state and as cholesterol ester, the relative proportion being, free, 25-50%; ester, 50-80%. It seems that in childhood myxedema not only is the total cholesterol increased but at times the ratio of ester to free cholesterol is reversed as was found by the authors in 7 of their cases. The total amount of cholesterol and the ratio may become normal after intensive treatment with thyroid extract.—M. B. G.

Basal metabolism in asthma and epilepsy. Topper, A. and H. Mulier, Am. J. Dis. Child. **46:** 963. 1933.

The results of basal metabolic tests on 25 children with asthma and 25 children with epilepsy are reported. All of the children with asthma showed a normal B.M.R. (within plus or minus 10) but the majority were minus readings. Of the children with epilepsy, 24 had a normal B.M.R. but the majority showed minus readings. The basal metabolic rate of children suffering from epilepsy or asthma tends to be lowered. The lowered rate of metabolism should not be considered as an indication for the use of thyroid extract or thyroxine. It may be explained on the basis of a reduced amount of thyroxine in the tissues due to excessive demands made on the thyroid gland during the spasmodic upheavals which occur periodically in these two conditions and therefore is an effect rather than a cause of epilepsy and asthma.—M. B. G.

Hepatic pathology in exophthalmic goiter. Weller, C. V., Ann. Int. Med. **7:** 543. 1933.

That the liver may be, and frequently is, involved in Graves' disease is shown clinically by the occasional occurrence of icterus, marked degrees of which are known to be of serious import in this disease; physiologically, by the accumulating evidence of altered liver function in such patients; experimentally, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxine, and morphologically, by structural changes in the liver, varying from slight degrees of chronic hepatitis to a widespread degenerative and necrotizing process which must be considered an "acute

yellow atrophy." In a series of 48 carefully selected cases of Graves' disease well-marked hepatitis was found in 54%; while a matched control series of the same size yielded but a single case (2%) with well-marked hepatitis. As usually seen, this liver lesion is interlobular, is patchily distributed, involves the peripheral portion of the lobules to a moderate degree, and shows relatively more fibrosis and lymphocyte infiltration than bile duct proliferation. It may be characterized as a patchy chronic parenchymatous interlobular hepatitis. Correlation with the severity and duration of thyrotoxicosis is indicated, but as yet unproved.—Author's Summary.